Literature update week 03 (2020)

[1] *Almeida JT, Esteves AL, Martins F, Palma I*. **[Approach to Patients with Statin Intolerance: Evidence-Based Review]**. Acta medica portuguesa 2020; 33:49-57.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31928603
ABSTRACT
INTRODUCTION: Statins are among the most effective drugs in lowering cholesterol levels and, consequently, in reducing cardiovascular mortality and morbidity. Although generally well tolerated, they have adverse effects that may reduce patient adherence to therapy. The objective of this evidence-based review is to summarize the evidence on the effectiveness of alternative management strategies in patients with intolerance to statins. MATERIAL AND METHODS: A literature search including clinical practice guidelines, systematic reviews and meta-analyses was conducted, in January 2017, in major international databases, and considered articles published in the last 10 years. The search was complemented with research papers published over the past three years and found in the PubMed database. The level of evidence and strength of recommendation were determined using the scale Strength of Recommendation Taxonomy - SORT. RESULTS: We included eight guidelines, six systematic reviews and one research paper. DISCUSSION: The strategies proposed by the different studies vary according to the severity of symptoms of intolerance including maintenance of the statin therapy (dose reduction, addition of a statin of equal or lower intensity or alternate days' uptake) and lipid-lowering therapy with other drugs (ezetimibe monotherapy or association with statin tolerated dose). Supplementation with coenzyme Q10 or vitamin D, in order to improve adherence to treatment with statins, is not recommended. CONCLUSION: This review highlights some alternatives to address patients' intolerance to statins; however, these are mostly based on recommendations with low to moderate evidence. Therefore, further research with randomized studies involving greater number of patients is required, in order to obtain a more robust recommendation.

[2] *Wang C, Wang F, Cao Q et al.* **Effect and safety of combination lipid-lowering therapies based on statin treatment versus statin monotherapies on patients with high risk of cardiovascular events**. Aging medicine (Milton (N.S.W)) 2018; 1:176-184.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31942495
ABSTRACT
This study aimed to compare the effect and safety of statin monotherapies and combination therapies on lipid-lowing therapies. We searched for published randomized controlled trial (RCT) reports of statin monotherapies and combination therapies in patients with high risk of cardiovascular events, and extracted lipid levels to perform meta-analysis. A total of 12 RCT reports were included in this study. According to the new guidelines (low-density lipoprotein cholesterol [LDL-C] < 100 mg/dL, high-density lipoprotein cholesterol [HDL-C] > 130 mg/dL), the percent of LDL-C attaining goals in combination therapy is more than that of monotherapy (risk ratio [RR] = 1.43, 95% confidence interval [CI]: 1.13 to 1.82, P = 0.003), and the percent of LDL-C and HDL-C attaining goals in combination therapy is greater than that of monotherapy (RR = 1.43, 95% CI: 1.24 to 1.65, P = 0.000). The changing level of blood lipid had significant statistical difference between the two groups. The degree of blood lipid lowered by combination therapy was larger than in monotherapy (standard mean difference [SMD] = -0.45, 95% CI: -0.75 to -0.14, P = 0.004; SMD = -0.72, 95% CI: 0.04 to 1.39, P = 0.039; and SMD = -0.71, 95% CI: -1.12 to -0.3, P = 0.001 in LDL-C, HDL-C, and triglyceride, respectively). The incidence of adverse events was not significantly different between

the two groups (RR = 1.15, 95% CI: 0.91 to 1.37, P = 0.096; RR = 1.5, 95% CI: 0.55 to 4.1, P = 0.427; RR = 0.63, 95% CI: 0.33 to 1.24, P = 0.181 in incidence of total adverse events, drug-related treatment, and myalgia, respectively). Combination therapy can bring better effect in reducing lipid. It does not increase the incidence of adverse events, so it can be used widely and safely.

[3] *Salahuddin T, Kittelson J, Tardif JC et al.* **Association of high-density lipoprotein particle concentration with cardiovascular risk following acute coronary syndrome: A case-cohort analysis of the dal-Outcomes trial**. American heart journal 2019; 221:60-66.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31927126
ABSTRACT
BACKGROUND: High-density lipoprotein cholesterol (HDL-C) concentration is inversely related to risk of major adverse cardiovascular events (MACE) in epidemiologic studies but is a poorer predictor of MACE in patients with established coronary heart disease. HDL particle concentration (HDLP) has been proposed as a better predictor of risk. We investigated whether HDLP is associated with risk of MACE after acute coronary syndrome (ACS). METHODS: The dal-Outcomes trial compared the CETP inhibitor dalcetrapib with placebo in patients with recent ACS. In a nested case-cohort analysis, total, large, medium, and small HDLPs were measured by nuclear magnetic resonance spectroscopy at baseline (4-12weeks after ACS) in 476 cases with MACE and 902 controls. Hazard ratios (HRs; case-control) for 1-SD increment of HDLP or HDL-C at baseline were calculated with and without adjustment for demographic, clinical, laboratory, and treatment variables. Similarly, HRs for MACE were calculated for changes in HDLP or HDL-C from baseline to month 3 of assigned treatment. RESULTS: Over median follow-up of 28months, the risk of MACE was not associated with baseline HDLP (adjusted HR=0.98, 95% CI=0.84-1.15, P=.81), any HDLP subclass, or HDL-C. Dalcetrapib increased HDL-C and total, medium, and large HDLP and decreased small HDLP but had no effect on MACE compared with placebo. There were no association of risk of MACE with change in HDLP or HDL-C and no interaction with assigned study treatment. CONCLUSIONS: Neither baseline HDLP nor the change in HDLP on treatment with dalcetrapib or placebo was associated with risk of MACE after ACS.

[4] *Jia X, Ramsey DJ, Rifai MA et al.* **Impact of Lipid Monitoring on Treatment Intensification of Cholesterol Lowering Therapies (from the Veterans Affairs Healthcare System)**. The American journal of cardiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31952841
ABSTRACT
Treatment guidelines recommend monitoring of lipids to assess efficacy and adherence to lipid lowering therapy. We assessed whether lipid profile monitoring is associated with intensification of cholesterol lowering therapy. Patients from the Veterans Affairs (VA) healthcare system with atherosclerotic cardiovascular disease and at least one primary care visit between October 2013 and September 2014 were included (n=1,061,753). Treatment intensification was defined as the initiation of a statin, an increase in the intensity or dose of statin therapy and/or the addition of ezetimibe. An association between the number of lipid panels and treatment intensification was assessed with adjusted regression models. During the study period, 87.1% of included patients had >/=1 lipid panel. Patients with >/=1 lipid panel were more likely to undergo treatment intensification compared with individuals with 0 lipid panels (9.3% vs 5.4%, respectively, p <0.001).

Among individuals not on statin therapy at the index date (n=287,636), those with >/=1 lipid panel were more likely to have a statin initiated compared those who without a lipid panel (21.5% vs 8.7%, p <0.001). On regression analysis (odds ratio [OR] [95% confidence interval {CI}]), patients with 1 lipid panel (1.55 [1.50 to 1.59]), 2 to 3 lipid panels (1.76 [1.71 to 1.81]) and >3 lipid panels (3.02 [2.90 to 3.14]) showed greater odds of treatment intensification compared with individuals without a lipid panel. In conclusion, lipid monitoring is associated with higher rates of treatment intensification in patients with atherosclerotic cardiovascular disease. This has important clinical implications as higher intensity regimens with statins and in combination with select nonstatin therapies is associated with improved cardiovascular outcomes.

[5] *Krempf M, Hopkins PN, Bruckert E et al.* **Efficacy and Safety of Alirocumab in Patients With Autosomal Dominant Hypercholesterolemia Associated With Proprotein Convertase Subtilisin/Kexin Type 9 Gain-of-Function or Apolipoprotein B Loss-of-Function Mutations**. The American journal of cardiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31932084
ABSTRACT
Autosomal dominant hypercholesterolemia results from mutations affecting the low-density lipoprotein receptor pathway, including proprotein convertase subtilisin/kexin type 9 (PCSK9) gain-of-function mutations (GoFm) and apolipoprotein B (APOB) loss-of-function mutations (LoFm). This study examined the long-term efficacy and safety of alirocumab in patients with PCSK9 GoFm and APOB LoFm who participated in the open-label extension to a Phase 2 double-blind study (NCT01604824). Of the 23 patients who completed the 14-week double-blind period and 8-week follow-up, 21 opted to continue in the open-label extension (PCSK9 GoFm, n=15; APOB LoFm, n=6). Patients received alirocumab 150 mg every 2 weeks from week 32 up to 3 years for PCSK9 GoFm and 2 years for APOB LoFm. Mean duration of alirocumab exposure was 129 weeks (median: 144 weeks). After initiation of alirocumab treatment, low-density lipoprotein cholesterol (LDL-C) decreased in both groups. At week 80, mean percent reduction in LDL-C from baseline was 58.0% and 47.1% for PCSK9 GoFm and APOB LoFm groups, respectively. Treatment-emergent adverse events were reported in 19 patients (90.5%); no patients discontinued treatment due to treatment-emergent adverse events. In patients with autosomal dominant hypercholesterolemia and elevated LDL-C levels despite receiving maximally tolerated lipid-lowering therapies, alirocumab 150 mg every 2 weeks resulted in clinically meaningful reductions in LDL-C, sustained through to 3 years and 2 years for patients with PCSK9 GoFm and APOB LoFm, respectively. Alirocumab was generally well tolerated with no unexpected safety concerns.

[6] *Santos DM, Pantano L, Pronzati G et al.* **Screening for YAP Inhibitors Identifies Statins as Modulators of Fibrosis**. Am J Respir Cell Mol Biol 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31944822
ABSTRACT
Idiopathic pulmonary fibrosis (IPF) is a lung disease with limited therapeutic options characterized by pathological fibroblast activation and aberrant lung remodeling with scar formation. Yes associated protein (YAP) is a transcriptional co-activator that mediates mechanical and biochemical signals controlling fibroblast activation. In this study, we developed a high-throughput small molecule screen for YAP inhibitors in primary human lung fibroblasts (HLF). Multiple hydroxy-3-

methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) were found to inhibit YAP nuclear localization via induction of YAP phosphorylation, cytoplasmic retention and degradation. We further show that the mevalonate pathway regulates YAP activation, and that simvastatin treatment reduces fibrosis markers in activated HLF and in the bleomycin mouse model of pulmonary fibrosis. Finally, we show simvastatin modulates YAP in vivo in mouse lung fibroblasts. Our results highlight the potential of small molecule screens for YAP inhibitors and provide a mechanism for the anti-fibrotic activity of statins in IPF.

[7] *Kaushik A, Kapoor A, Agarwal SK et al.* **Statin reload before off-pump coronary artery bypass graft: Effect on biomarker release kinetics**. Annals of cardiac anaesthesia 2020; 23:27-33.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31929243
ABSTRACT
Objectives: Statins confer protection from ischemia/reperfusion through various pathways including pleiotropic mechanisms. Following chronic administration, activation of intrinsic cellular mechanisms causes attenuation of these pleiotropic effects. Methods: Since coronary artery bypass surgery (CABG) represents a reversible ischemia-reperfusion sequence, we assessed if statin reload is effective in patients undergoing off-pump CABG (n = 100) in limiting myocardial injury. Patients received loading dose of rosuvastatin (40 mg initiated 7 days before surgery) while nonloaded patients continued whatever statin dose they were receiving and served as controls. Cardiac biomarkers (Troponin-I, creatine kinase muscle/brain [CK-MB], and B-type natriuretic peptide [BNP]) were measured at 8, 24, and 48 h postoperatively. The primary end-point was the extent of perioperative myocardial injury (area under the curve [AUC]: AUC of each biomarker). Results: Despite similar baseline levels, all biomarkers at 8, 24, and 48 h were significantly lower in the loaded group. The AUC for each biomarker was also significantly lower in the loaded group (cTnI 37.96 vs. 70.12 ng. hr/ml, CK-MB 229.64 vs. 347.04 ng. hr/ml, and BNP 5257.56 vs. 15606.68 pg. hr/ml, all P < 0.001). Delta cTnI (change from baseline to peak level) (1.00 +/- 1.34 vs. 2.25 +/- 2.59), delta CK-MB (4.54 +/- 5.89 vs. 10.68 +/- 9.95), and delta BNP (120.41 +/- 172.48 vs. 449.23 +/- 790.95) all P < 0.001 were also significantly lower in the loaded group. Those loaded with rosuvastatin had lower inotrope duration (22.9 +/- 23.33 vs. 31.26 +/- 25.39 h, P = 0.04) and ventilator support time (16.94 +/- 6.78 vs. 23.8 +/- 20.53 h, P = 0.03). Conclusion: In patients undergoing off-pump CABG, statin reload can "recapture" cardioprotection in patients already on statins with favorable effect on release kinetics of biomarkers and postoperative outcomes.

[8] *Nordestgaard BG, Langlois MR, Langsted A et al.* **Quantifying atherogenic lipoproteins for lipid-lowering strategies: Consensus-based recommendations from EAS and EFLM**. Atherosclerosis 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31928713
ABSTRACT
The joint consensus panel of the European Atherosclerosis Society (EAS) and the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) recently addressed present and future challenges in the laboratory diagnostics of atherogenic lipoproteins. Total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and calculated non-HDL cholesterol (=total - HDL cholesterol) constitute the primary lipid panel for estimating risk of atherosclerotic cardiovascular disease (ASCVD) and can be measured in the nonfasting state. LDL cholesterol is the primary target

of lipid-lowering therapies. For on-treatment follow-up, LDL cholesterol shall be measured or calculated by the same method to attenuate errors in treatment decisions due to marked between-method variations. Lipoprotein(a)-cholesterol is part of measured or calculated LDL cholesterol and should be estimated at least once in all patients at risk of ASCVD, especially in those whose LDL cholesterol decline poorly upon statin treatment. Residual risk of ASCVD even under optimal LDL-lowering treatment should be also assessed by non-HDL cholesterol or apolipoprotein B, especially in patients with mild-to-moderate hypertriglyceridemia (2-10 mmol/L). Non-HDL cholesterol includes the assessment of remnant lipoprotein cholesterol and shall be reported in all standard lipid panels. Additional apolipoprotein B measurement can detect elevated LDL particle numbers often unidentified on the basis of LDL cholesterol alone. Reference intervals of lipids, lipoproteins, and apolipoproteins are reported for European men and women aged 20-100 years. However, laboratories shall flag abnormal lipid values with reference to therapeutic decision thresholds.

[9] *Bonaventura A, Grossi F, Montecucco F*. **PCSK9 is a promising prognostic marker in patients with advanced NSCLC**. Cancer immunology, immunotherapy : CII 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31938855
ABSTRACT

[10] *Cordes T, Metallo CM*. **Statins Limit Coenzyme Q Synthesis and Metabolically Synergize with MEK Inhibition in Pancreatic Tumors**. Cancer research 2020; 80:151-152.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31941676
ABSTRACT
Tumors frequently increase expression of enzymes in the mevalonate biosynthesis pathway. Statins inhibit flux through this pathway, but if and how such treatments elicit a therapeutic benefit in cancer remains unclear. In this issue of Cancer Research, McGregor and colleagues perform in vivo metabolic tracing to demonstrate that mouse pancreatic ductal adenocarcinoma (PDAC) tumors and human PDAC cell lines require this pathway for coenzyme Q (CoQ) synthesis and redox homeostasis. Simvastatin treatment reduces CoQ synthesis and promotes oxidative stress and apoptosis in tumors when administered in combination with a MEK inhibitor, providing a new mechanism through which statin treatment may impact PDAC growth.See related article by McGregor et al., p. 175.

[11] *Williams B, Masi S, Wolf J, Schmieder RE*. **Facing the Challenge of Lowering Blood Pressure and Cholesterol in the Same Patient: Report of a Symposium at the European Society of Hypertension**. Cardiology and therapy 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31933276
ABSTRACT
A symposium held at the 29th European Meeting on Hypertension and Cardiovascular Protection in Milan, Italy, discussed the potential impact and long-term benefits of early active management of cardiovascular disease (CVD) risk in patients with hypertension, and potential barriers to this strategy. Hypertension often aggregates with other cardiovascular risk factors, exponentially increasing morbidity and mortality. While effective therapies to treat hypertension exist, a substantial number of patients still experience major cardiovascular events. Two major issues account for these disappointing results: interventions initiated too late in the disease trajectory and

lack of effective translation of the research findings into daily clinical practice. Results from genetic studies suggest that lifetime exposure to lower blood pressure (BP) and cholesterol levels due to protective gene mutations, can provide greater cardiovascular benefits than middle-/late-age interventions. Clinical guidelines suggest adding statins to BP-lowering therapies for further cardiovascular benefits in most hypertensive patients; however, real-world data show that physicians' compliance with these recommendations and patients' adherence to BP- and lipid-lowering treatments remain poor, resulting in poor risk factor control and an increased risk of adverse outcomes. The use of single-pill combinations (SPC) can partially mitigate these issues, as they are associated with increased patient adherence and improved BP control. Treatment with SPC has been recommended in the European Hypertension Guidelines, but optimization of the total CVD risk may need adoption of more ambitious treatment strategies aimed to deliver single pills that control multiple CVD risk factors. Amlodipine, perindopril and atorvastatin have been shown to improve BP and lipid levels to a great extent when given separately, and this combination has also been shown to improve cardiovascular outcomes. Overall, early intervention in patients with hypertension with use of an effective, high-intensity cardiovascular risk reduction regimen and attention to medication adherence through reducing pill burden are likely to result in optimal outcomes.

[12] *Tanaka A, Nakamura T, Sato E et al.* **Effect of pemafibrate, a novel selective peroxisome proliferator-activated receptor-alpha modulator (SPPARMalpha), on urinary protein excretion in IgA nephropathy with hypertriglyceridemia**. CEN case reports 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31950425
ABSTRACT
Lipid abnormalities, including hypertriglyceridemia, are one of the most common comorbidities in patients with chronic kidney disease (CKD) and are independently associated with disease progression. However, it remains uncertain whether treatment for hypertriglyceridemia has favorable effects on the clinical course of IgA nephropathy (IgAN). Pemafibrate is a novel selective peroxisome proliferator-activated receptor-alpha modulator and may be distinct from conventional fibrates in terms of its pharmacological activity and hepatic and renal safety. A recent clinical study demonstrated that pemafibrate was safe and effective for correcting pro-atherogenic lipid abnormalities in CKD patients with a wide range of renal insufficiency. However, the effect of pemafibrate on renal function in patients with IgAN and hypertriglyceridemia has not been verified. This paper is the first to show that 12 months of pemafibrate (0.1 mg daily) administration in three drug-naive and mild IgAN patients with variable renal dysfunction and histopathology proven IgAN decreased serum triglyceride level and excretion of urinary protein and liver-type fatty acid-binding protein with no change in estimated glomerular filtration rate (eGFR). These findings suggest that pemafibrate is safe and effective for correcting hypertriglyceridemia and decreasing urinary protein excretion without changing eGFR and blood pressure levels in mild IgAN patients with hypertriglyceridemia.

[13] *Lechea E, Popescu M, Dimulescu D et al.* **The Impact of Bariatric Surgery on Diabetes and Other Cardiovascular Risk Factors**. Chirurgia (Bucharest, Romania : 1990) 2019; 114:725-731.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31928577
ABSTRACT

Introduction: Nowadays, obesity is a major worldwide health problem due to its serious consequences and toits increasing prevalence. Bariatric surgery has demonstrated a sustained weight loss and an efficient long-term control of the co-morbidities associated with obesity. The objective of our study was to compare cardiovascular risk factors before and after bariatric surgery. Material and Method: We have retrospectively studied 59 consecutive patients scheduled for bariatric surgery (gastric sleeve) in Ponderas Academic Hospital between January and March 2016, excluding the ones that didn't commit to respect the follow-up terms. The preoperative, 6 and 12 postoperative months blood tests and anthropometric measurements were comparatively analyzed. Results: BMI, waist circumference and total body weight decreased by 38%, 31%, and 41%; Glycemia, triglycerides and LDL cholesterol decreased by 16%, 37% and 9% respectively; HDL cholesterol increased by 18%. The decline was statistically significant for all variables (P 0.001) except for LDL cholesterol. The need for antihypertensive treatment was reduced by 60% and for lipid lowering treatment diminished by 21%. In diabetic patients glycated hemoglobin (HbA1c) decreased by 28% and the necessity for antidiabetic medical treatment dropped by 69%. Conclusions: Weight loss obtained by bariatric surgery in this study, improved the metabolic syndrome in all its components, obesity, hyperglycemia/type 2 diabetes, hypertension, and dyslipidemia, thus reducing the cardiovascular risk.

[14] *Neelakantan N, Seah JYH, van Dam RM*. **The Effect of Coconut Oil Consumption on Cardiovascular Risk Factors: A Systematic Review and Meta-Analysis of Clinical Trials**. Circulation 2020.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31928080

ABSTRACT

Background: Coconut oil is high in saturated fat and may, therefore, raise serum cholesterol concentrations, but beneficial effects on other cardiovascular risk factors have also been suggested. Therefore, we conducted a systematic review of the effect of coconut oil consumption on blood lipids and other cardiovascular risk factors compared with other cooking oils using data from clinical trials. Methods: We searched PubMed, SCOPUS, Cochrane Registry, and Web of Science through June 2019. We selected trials that compared the effects of coconut oil consumption with other fats that lasted at least 2 weeks. Two reviewers independently screened articles, extracted data, and assessed the study quality according to the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). The main outcomes included low-density lipoprotein cholesterol (LDL-cholesterol), high-density lipoprotein cholesterol (HDL-cholesterol), total cholesterol, triglycerides, measures of body fatness, markers of inflammation, and glycemia. Data were pooled using random-effects meta-analysis. Results: 16 articles were included in the meta-analysis. Results were available from all trials on blood lipids, 8 trials on body weight, 5 trials on percentage body fat, 4 trials on waist circumference, 4 trials on fasting plasma glucose, and 5 trials on C-reactive protein. Coconut oil consumption significantly increased LDL-cholesterol by 10.47 mg/dL (95% CI: 3.01, 17.94; I(2) = 84%, N=16) and HDL-cholesterol by 4.00 mg/dL (95% CI: 2.26, 5.73; I(2) = 72%, N=16) as compared with nontropical vegetable oils. These effects remained significant after excluding nonrandomized trials, or trials of poor quality (Jadad score <3). Coconut oil consumption did not significantly affect markers of glycemia, inflammation, and adiposity as compared with nontropical vegetable oils. Conclusions: Coconut oil consumption results in

significantly higher LDL-cholesterol than nontropical vegetable oils. This should inform choices about coconut oil consumption.

[15] *Kim EJ, Wierzbicki AS*. **Cardiovascular prevention: Frontiers in lipid guidelines**. Clinical medicine (London, England) 2020; 20:36-42.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31941730
ABSTRACT
Cardiovascular disease (CVD) remains one of the principal causes of morbidity and mortality in the world. International guidelines are being updated to take into account new evidence and improved health economics as drug patents expire. Recent studies have investigated the best lipid fractions to predict CVD, suggested additional CVD risk factors and a potential role for novel biomarkers while big data approaches have allowed improvements to be made to CVD risk calculators. The increasing availability of next generation sequencing is allowing systematic efforts to be made to detect monogenic familial hypercholesterolaemia.Previous trials have validated the low-density lipoprotein cholesterol (LDL-C) hypothesis of atherosclerosis. Statins now form part of universal treatment advice for CVD and trial data on ezetimibe also suggests it has a place in the treatment pathway. New data has been published on novel lipid-lowering therapies such as proprotein convertase subtilisin kexin 9 inhibitors but the role of these expensive drugs has yet to be fully settled and a diversity of approaches exists between guidelines.The role of lipid fractions outside LDL-C is unclear. There will be challenges in incorporating new non-linear data on omega-3 fatty acids that not only affect triglycerides but more directly CVD.

[16] *Karageorgos GM, Apostolakis IZ, Nauleau P et al.* **Atherosclerotic plaque mechanical characterization coupled with vector Doppler imaging in atherosclerotic carotid arteries in-vivo**. Conference proceedings : ... Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Annual Conference 2019; 2019:6200-6203.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31947259
ABSTRACT
Methods used in clinical practice to diagnose and monitor atherosclerosis present limitations. Imaging the mechanical properties of the arterial wall has demonstrated the potential evaluate plaque vulnerability and assess the risk for stroke. Adaptive Pulse Wave Imaging (PWI) is a non-invasive ultrasound imaging technique, which automatically detects points of spatial mechanical inhomogeneity along the imaged artery and provides piecewise stiffness characterization. The aims of the present study are to: 1) demonstrate the initial feasibility of adaptive PWI to image the mechanical properties of an atherosclerotic plaque 2) demonstrate the feasibility to combine adaptive PWI with vector Doppler in a single imaging modality in order to simultaneously obtain information plaque mechanical properties and plaque hemodynamics. The common carotid arteries of 1 healthy subject and 2 carotid artery disease patients were scanned in vivo. One of the patients underwent carotid endarterectomy and a plaque sample was retrieved. In this patient, a higher compliance value of the stenotic segment was estimated by Adaptive PWI as compared with the adjacent arterial wall, and the healthy carotid artery. This was corroborated by histological staining of the plaque sample, which revealed the presence of a large necrotic core and a thrombus, characteristics associated with reduced stiffness. Moreover, the same sequence

demonstrated the feasibility to obtain both stiffness maps and vector flow information, showing promise in atherosclerosis diagnosis and patient care.

[17] *Oweis GF*. **An in Vitro Flow Model for Cardiovascular Inflammation**. Conference proceedings : ... Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Annual Conference 2019; 2019:5014-5017.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31946986
ABSTRACT
Cardiovascular disease is modern-day plague with a vast number of lives claimed, and an enormous socio-economic cost incurred. Hemodynamics of the cardiovascular system play an important mechanistic role in disease development. For instance, atherosclerotic plaque depositions are often correlated with regions of turbulent flow patterns and disturbed hemodynamic shear stress. A simplified, rigid, in vitro, flow model of a real-size aortic arch is described. The flow in the arched vessel is attached and healthy at the outer curvature, while it is separated and disturbed at the inner curvature wall, which is an ideal setting to study cardiovascular disease. Endothelial cells can be cultured on the lumen of the aortic arch model under controlled flow conditions and extracted from the inner and outer curvature walls for biochemical signaling studies. The flow velocity field in the model is characterized using particle image velocimetry PIV which allows for the estimation of the wall shear stress. This helps in correlating the underlying hemodynamics to the biomechanical response of the endothelium.

[18] *Pleouras D, Rocchiccioli S, Pelosi G et al.* **A computational multi-level atherosclerotic plaque growth model for coronary arteries**. Conference proceedings : ... Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Annual Conference 2019; 2019:5010-5013.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31946985
ABSTRACT
In this work, we present a novel computational approach for the prediction of atherosclerotic plaque growth. In particular, patient-specific coronary computed tomography angiography (CCTA) data were collected from 60 patients at two time points. Additionally, blood samples were collected for biochemical analysis. The CCTA data were used for 3D reconstruction of the coronary arteries, which were then used for computational modeling of plaque growth. The model of plaque growth is based on a multi-level approach: i) the blood flow is modeled in the lumen and the arterial wall, ii) the low and high density lipoprotein and monocytes transport is included, and iii) the major atherosclerotic processes are modeled including the foam cells formation, the proliferation of smooth muscle cells and the formation of atherosclerotic plaque. Validation of the model was performed using the follow-up CCTA. The results show a correlation of the simulated follow-up arterial wall area to be correlated with the corresponding realistic follow-up with r(2)=0.49, P<; 0.0001.

[19] *Rajasekaran C, Jayanthi KB, Sudha S, Kuchelar R*. **Automated Diagnosis of Cardiovascular Disease Through Measurement of Intima Media Thickness Using Deep Neural Networks**. Conference proceedings : ... Annual International Conference of the IEEE Engineering in Medicine

and Biology Society. IEEE Engineering in Medicine and Biology Society. Annual Conference 2019; 2019:6636-6639.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31947363
ABSTRACT
Ultrasound images(US) of carotid artery aid in the detection and diagnosis of Cardiovascular Diseases (CVD). Traditional methods for analysis of US images employ hand crafted features to classify images, which need expert knowledge for careful design and lack robustness to variations, leading to low sensitivity in clinical applications. Intima Media Thickness (IMT) and elasticity are the predominant markers used for carotid artery (CA) atherosclerotic plaque detection. This paper proposes to address the problem by building Convolutional Neural Network (CNN) for segmentation of intima media complex (ie) Region of Interest (RoI). A dataset consisting of 450 subjects is used to train and validate the proposed CNN. Segmentation is done in the far wall region of the artery from the longitudinal B-mode images enabling atleast 24 RoIs and RoNIs (Region of Non Interest) for each image. The result of 10-fold cross validation shows accuracy of 99.54%. Mean deviation of IMT from manual tracings is found to be 0.06645mm.

[20] *Mehta A, Mahtta D, Gulati M et al.* **Cardiovascular Disease Prevention in Focus: Highlights from the 2019 American Heart Association Scientific Sessions**. Current atherosclerosis reports 2020; 22:3.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31927694
ABSTRACT
PURPOSE OF THE REVIEW: This review highlights selected cardiovascular disease (CVD) prevention studies presented at the 2019 American Heart Association (AHA) Scientific Sessions. RECENT FINDINGS: Several important cardiovascular prevention studies were presented at the 2019 AHA Scientific Sessions. Results from the Colchicine Cardiovascular Outcomes Trial (COLCOT) showed that low-dose colchicine reduces the risk of recurrent CVD events among patients with recent myocardial infarction. A prospective analysis from the UK Biobank cohort demonstrated that the increased CVD risk associated with clonal hematopoiesis of indeterminate potential is mitigated by a common disruptive mutation in the IL6R gene that suppresses the pro-inflammatory IL-1beta/IL-6 pathway. The Treat Stroke to Target trial demonstrated that reducing low-density lipoprotein cholesterol to <70 mg/dL among patients with ischemic stroke or transient ischemic attack reduces the risk of recurrent CVD events as compared with a higher LDL-C target of 90-110 mg/dL. A secondary analysis focusing on American participants enrolled in the Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT) showed that these patients receive a similar benefit in terms of cardiovascular risk reduction with icosapent ethyl as compared with the entire trial population. A post hoc analysis of the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial demonstrated that a genetic risk score comprising 27 single-nucleotide polymorphisms is associated with cardiovascular risk among patients with established atherosclerotic CVD and patients with high genetic risk receive a relatively higher benefit from evolocumab use. Similar results were observed with alirocumab use in a post hoc analysis of the ODYSSEY OUTCOMES trial where a genome-wide polygenic risk score comprising 6.5 million DNA variants was used. These studies presented at 2019 AHA Scientific Sessions will help guide our approach to preventing CVD.

[21] *AlKhalil M, Al-Hiari Y, Kasabri V et al.* **Selected pharmacotherapy agents as antiproliferative and anti-inflammatory compounds**. Drug development research 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31943302
ABSTRACT
The repurposing of safe therapeutic drugs has emerged as an alternative approach to rapidly identify effective, safe, and conveniently available therapeutics to treat/prevent cancer. Therefore, it was hypothesized that acidic chelator drugs could have a genuine potential as antiproliferative agents. Based on their pKa, the selected 15 acidic drugs of eight classes-namely sulfonylureas, proton pump inhibitors, fluoroquinolones, nonsteroidal anti-inflammatory agents, thiazolidinediones, thienopyridines, statins, and nicotinic acid-were assayed for anticancer HTS against the lung A549, skin A375, breast MCF7 and T47D, pancreatic PANC1, cervical HeLa, and leukemia K562 cancer cell lines and normal fibroblasts. Lipopolysaccharide-prompted inflammation in RAW264.7 macrophages was the potential anticancer mechanism. Atorvastatin exerted remarkably superior cytotoxicity against A375.2S (IC50 value 0.02 muM $p < .001$ vs. cisplatin 0.07 muM IC50 value). Atorvastatin exhibited an equipotency to cisplatin's T47D growth inhibition (34.6 muM vs. 34.59 muM; $p > .05$). Levofloxacin as well as ciprofloxacin superbly superseded the antineoplastic cisplatin activity against the K562 cell line (respective IC50 values [muM] 10.4 and 19.5 vs. 29.3; $p < .05$-$<.01$). Gemifloxacin and lansoprazole had comparable antiproliferation in K562 to cisplatin's (respective IC50 values [muM] 34.9 and 36.3 vs. 29.3; $p > .05$). The selected agents lacked cytotoxicity in the panel of MCF7, HeLa, A549, or Panc1 cancer cells. Most notably, LPS prompted RAW264.7 macrophages, atorvastatin, piroxicam, clopidogrel, esomeprazole, and lansoprazole were of higher anti-inflammation potency than indomethacin ($p < .01$-$.001$). Evidently, omeprazole, pioglitazone, gemifloxacin, and indomethacin were of comparable anti-inflammation potencies ($p > .05$). Collectively, this work reveals acidic chelator drugs (atorvastatin, gemifloxacin, and lansoprazole with dual anti-inflammation and antiproliferation propensities) as authentic agents for the repurposing approach in anticancer chemotherapy/prevention.

[22] *Weng S, Luo Y, Zhang Z et al.* **Effects of metformin on blood lipid profiles in nondiabetic adults: a meta-analysis of randomized controlled trials**. Endocrine 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31950354
ABSTRACT
PURPOSE: To evaluate the effects of metformin on serum lipid profiles in nondiabetic adults through a comprehensive meta-analysis. METHODS: In the present meta-analysis, randomized and controlled trials were collected by searching PubMed, Embase, and Cochrane Libraries from inception to April 2019. Compared with placebos, the effects of metformin treatment on lipid profiles in nondiabetic adults were evaluated. RESULTS: Forty-seven studies from 45 articles including 5731 participants were enrolled. Pooled results showed that metformin had significant effects on total cholesterol (mean change -6.57 mg/dl; 95% CI -9.66, -3.47; P = 0.000) and LDL-c (mean change -4.69 mg/dl; 95% CI -7.38, -2.00; P = 0.001), but insignificant effects on HDL-c (mean change -4.33 mg/dl; 95% CI -9.62, 0.96; P = 0.109) and triglyceride (mean change -0.85 mg/dl; 95% CI -0.36, 2.06; P = 0.169). Significant heterogeneities were found for all lipid profiles (HDL-c = 85.5%; LDL-c = 59.9%; total cholesterol = 75.3% and triglyceride = 67.1%). Different from the pooled data, in a subgroup analysis, the effect of metformin on triglyceride in patients with polycystic ovarian syndrome (PCOS) was significant with a mean reduction of 8.15 mg/dl. In addition,

sensitivity analysis showed that the pooled effects of metformin on serum lipid profiles were stable. Publication bias derived from funnel plots or Begg's tests (P = 0.933, 0.860, 0.904, and 0.567 for HDL-c, LDL-c, total cholesterol, and triglyceride, respectively) was not significant. CONCLUSION: This meta-analysis revealed that metformin could reduce total cholesterol and LDL-c in nondiabetic adults. In addition, metformin might exert a triglyceride-lowering effect in nondiabetics with PCOS status.

[23] *Liu G, Zhang B, Hu Y et al.* **Associations of Perfluoroalkyl substances with blood lipids and Apolipoproteins in lipoprotein subspecies: the POUNDS-lost study**. Environmental health : a global access science source 2020; 19:5.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31931806
ABSTRACT
BACKGROUND: The associations of perfluoroalkyl substance (PFAS) exposure with blood lipids and lipoproteins are inconsistent, and existing studies did not account for metabolic heterogeneity of lipoprotein subspecies. This study aimed to examine the associations between plasma PFAS concentrations and lipoprotein and apolipoprotein subspecies. METHODS: The study included 326 men and women from the 2-year Prevention of Obesity Using Novel Dietary Strategies (POUNDS) Lost randomized trial. Five PFASs, including perfluorooctanesulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorohexanesulfonic acid (PFHxS), perfluorononanoic acid (PFNA), and perfluorodecanoic acid (PFDA), were measured in plasma at baseline. For lipoprotein and apolipoprotein subspecies, total plasma was fractionated first by apolipoprotein (apo) C-III content and then by density. Each subfraction was then measured for apoB, apoC-III, and apoE concentrations, as well as triglyceride and cholesterol contents, both at baseline and at 2 years. RESULTS: For lipids and apolipoproteins in total plasma at baseline, elevated plasma PFAS concentrations were significantly associated with higher apoB and apoC-III concentrations, but not with total cholesterol or triglycerides. After multivariate adjustment of lifestyle factors, lipid-lowering medication use, and dietary intervention groups, PFAS concentrations were primarily associated with lipids or apolipoprotein concentrations in intermediate-to-low density lipoprotein (IDL + LDL) and high-density lipoprotein (HDL) that contain apoC-III. Comparing the highest and lowest tertiles of PFOA, the least-square means (SE) (mg/dl) were 4.16 (0.4) vs 3.47 (0.4) for apoB (P trend = 0.04), 2.03 (0.2) vs 1.66 (0.2) for apoC-III (P trend = 0.04), and 8.4 (0.8) vs 6.8 (0.8) for triglycerides (P trend = 0.03) in IDL + LDL fraction that contains apoC-III. For HDL that contains apoC-III, comparing the highest and lowest tertiles of PFOA, the least-square means (SE) (mg/dl) of apoC-III were 11.9 (0.7) vs 10.4 (0.7) (P trend = 0.01). In addition, elevated PFNA and PFDA concentrations were also significantly associated with higher concentrations of apoE in HDL that contains apoC-III (P trend< 0.01). Similar patterns of associations were demonstrated between baseline PFAS concentrations and lipoprotein subspecies measured at 2 years. Baseline PFAS levels were not associated with changes in lipoprotein subspecies during the intervention. CONCLUSIONS: Our results suggest that plasma PFAS concentrations are primarily associated with blood lipids and apolipoproteins in subspecies of IDL, LDL, and HDL that contain apoC-III, which are associated with elevated cardiovascular risk in epidemiological studies. Future studies of PFAS-associated cardiovascular risk should focus on lipid subfractions.

[24] *Marques-Vidal P, Jankowski P, De Bacquer D, Kotseva K*. **Dietary measures among patients with coronary heart disease in Europe. ESC EORP Euroaspire V**. International journal of cardiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31937454
ABSTRACT
OBJECTIVE: Assess the dietary recommendations provided to patients hospitalized for a coronary heart disease (CHD) event. DESIGN: Cross-sectional, multicentre observational study (ESC EORP Euroaspire V). METHODS: 8261 participants (25.8% women, 9.3% aged<50 years) from 27 countries, 6 to 24 months after hospitalization for a CHD event were included. Participants were asked if they had been advised to reduce salt, fat or sugar intake, change type of fat consumed, and increase consumption of plant stanols/sterols, fruit & vegetables, fish and oily fish. Self-reported changes were recorded. RESULTS: Advice to reduce energy intake, salt, fat and sugar was provided to 64.5% [range: 9.2-90.5], 73.2% [38.6-95.2], 77.3% [42.3-95.6] and 67.0% [39.4-93.3] of patients, respectively. Advice to change fat type, increase consumption of plant stanols/sterols, fruit & vegetables, fish and oily fish was provided to 68.3% [33.7-92.3], 36.7% [0.6-75.2], 73.2% [39.2-93.6], 66.5% [8.0-90.8] and 53.5% [3.7-83.3] of patients, respectively. Advices were more frequently provided to patients aged 50 to 69, with a high educational level, or obesity. One-eighth [0-55.0] of patients reported having consulted a dietician. Reductions in energy intake, salt, fat and sugar were reported by 57.7% [4.9-81.0], 69.9% [32.1-85.9], 71.8% [40.4-88.4] and 61.2% [29.0-84.0] of patients, respectively. Changes in fat type and increased consumption of plant stanols/sterols, fruit & vegetables, fish and oily fish were reported by 60.9% [4.9-81.0], 25.8% [0.6-54.1], 69.2% [27.7-88.4], 54.8% [4.0-80.1] and 40.4% [2.0-66.8] of patients, respectively. CONCLUSION: Dietary advice is not systematically provided to patients with CHD, and considerable differences exist between European countries.

[25] *Di Taranto MD, Giacobbe C, Buonaiuto A et al.* **A Real-World Experience of Clinical, Biochemical and Genetic Assessment of Patients with Homozygous Familial Hypercholesterolemia**. Journal of clinical medicine 2020; 9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31947532
ABSTRACT
Homozygous familial hypercholesterolemia (HoFH), the severest form of familial hypercholesterolemia (FH), is characterized by very high LDL-cholesterol levels and a high frequency of coronary heart disease. The disease is caused by the presence of either a pathogenic variant at homozygous status or of two pathogenic variants at compound heterozygous status in the LDLR, APOB, PCSK9 genes. We retrospectively analyzed data of 23 HoFH patients (four children and 19 adults) identified during the genetic screening of 724 FH patients. Genetic screening was performed by sequencing FH causative genes and identifying large rearrangements of LDLR. Among the HoFH patients, four out of 23 (17.4%) were true homozygotes, whereas 19 out of 23 (82.6%) were compound heterozygotes for variants in the LDLR gene. Basal LDL-cholesterol was 12.9 +/- 2.9 mmol/L. LDL-cholesterol levels decreased to 7.2 +/- 1.8 mmol/L when treated with statin/ezetimibe and to 5.1 +/- 3.1 mmol/L with anti-PCSK9 antibodies. Homozygous patients showed higher basal LDL-cholesterol and a poorer response to therapy compared with compound heterozygotes. Since 19 unrelated patients were identified in the Campania region (6,000,000 inhabitants) in southern Italy, the regional prevalence of HoFH was estimated to be at least 1:320,000. In conclusion, our

results revealed a worse phenotype for homozygotes compared with compound heterozygotes, thereby highlighting the role of genetic screening in differentiating one genetic status from the other.

[26] *Li J, Li D, Yang D et al.* **Irregularity of Carotid Plaque Surface Predicts Subsequent Vascular Event: A MRI Study**. Journal of magnetic resonance imaging : JMRI 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31944452
ABSTRACT
BACKGROUND: The relationship between plaque compositions and irregular plaque surface and its predictive value for vascular events (VEs) are unknown. PURPOSE: To investigate the relationship between irregular carotid plaque surface and plaque compositional features and its predictive values for future VEs utilizing magnetic resonance (MR) vessel wall imaging. STUDY TYPE: Prospective study. POPULATION: In total, 140 patients with cerebrovascular symptoms were recruited. FIELD STRENGTH/SEQUENCE: 3T, black blood T1 -weighted, black blood T2 -weighted, 3D time-of-flight, magnetization-prepared rapid acquisition gradient echo (MP-RAGE), and 3D motion sensitized driven equilibrium rapid gradient echo (MERGE). ASSESSMENT: The carotid artery stenosis and maximum wall thickness (Max WT) were measured. The presence/absence of irregular carotid plaque surface, calcification, lipid-rich necrotic core (LRNC), intraplaque hemorrhage (IPH), and fibrous cap rupture was determined. After baseline examination, all patients were followed-up for at least 1 year to record the VEs. STATISTICAL TESTS: Independent t-test, Mann-Whitney U-test, Chi-square, logistic regression, and Cox regression were used. RESULTS: In total, 82 (58.6%) had irregular plaque surfaces. The carotid Max WT, stenosis, and the presence of surface calcification, LRNC and IPH were significantly associated with irregular plaque surface (all $P < 0.05$). After adjusted for baseline confounding factors, these associations remained statistically significant (all $P < 0.05$). During the median follow-up time of 12.1 months, 37 (26.4%) patients had VEs. Univariable Cox regression analysis showed that the irregular carotid plaque surface was significantly associated with subsequent VEs (hazard ratio [HR], 11.02; 95% confidence interval [CI], 2.65-45.85; $P = 0.001$). After adjusted for baseline and follow-up confounding factors, this association remained statistically significant (HR, 13.03; 95% CI, 1.71-99.42, $P = 0.013$). After further adjusted for intracranial stenosis, this association also remained statistically significant (HR, 12.57; 95% CI, 1.63-96.83, $P = 0.015$). DATA CONCLUSION: The morphology of carotid atherosclerotic plaque surface determined by MR vessel wall imaging, particularly irregular plaque surface, is an independent predictor for subsequent vascular events. LEVEL OF EVIDENCE: 1 Technical Efficacy Stage: 5 J. Magn. Reson. Imaging 2020.

[27] *He C, Wu Q, Hayashi N et al.* **Carbohydrate-restricted diet alters the gut microbiota, promotes senescence and shortens the life span in senescence-accelerated prone mice**. The Journal of nutritional biochemistry 2019; 78:108326.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31952014
ABSTRACT
This study examined the effects of a carbohydrate-restricted diet on aging, brain function, intestinal bacteria and the life span to determine long-term carbohydrate-restriction effects on the aging process in senescence-accelerated prone mice (SAMP8). Three-week-old male SAMP8 were divided into three groups after a week of preliminary feeding. One group was given a controlled

diet, while the others fed on high-fat and carbohydrate-restricted diets, respectively. The mice in each group were further divided into two subgroups, of which one was the longevity measurement group. The other groups fed ad libitum until the mice were 50 weeks old. Before the test period termination, passive avoidance test evaluated the learning and memory abilities. Following the test period, serum and various mice organs were obtained and submitted for analysis. The carbohydrate-restricted diet group exhibited significant decrease in the survival rate as compared to the other two diet groups. The passive avoidance test revealed a remarkable decrease in the learning and memory ability of carbohydrate-restricted diet group as compared to the control-diet group. Measurement of lipid peroxide level in tissues displayed a marked increase in the brain and spleen of carbohydrate-restricted diet group than the control-diet and high-fat diet groups. Furthermore, notable serum IL-6 and IL-1beta level (inflammation indicators) elevations, decrease in Enterobacteria (with anti-inflammatory action), increase in inflammation-inducing Enterobacteria and lowering of short-chain fatty acids levels in cecum were observed in the carbohydrate-restricted diet group. Hence, carbohydrate-restricted diet was revealed to promote aging and shortening of life in SAMP8.

[28] *Jensen TK, Priskorn L, Holmboe SA et al.* **Associations of Fish Oil Supplement Use With Testicular Function in Young Men**. JAMA network open 2020; 3:e1919462.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31951274

ABSTRACT

Importance: Many young men have poor semen quality, and the causes are often unknown. Supplement intake of omega-3 polyunsaturated fatty acid has been found to improve semen quality among men with infertility, but the association with semen quality among healthy men is unknown. Objective: To determine if intake of omega-3 fatty acid supplements is associated with testicular function as measured by semen quality and reproductive hormone levels among healthy men. Design, Setting, and Participants: This cross-sectional study included young Danish men from the general population recruited between January 1, 2012, and December 31, 2017, at compulsory examinations to determine their fitness for military service. Young unselected men were approached after the examination and invited to participate in a study of reproductive function, regardless of their fitness for military service. Data analysis was conducted from September 1, 2018, to June 30, 2019. Exposures: Intake of supplements, including fish oil, during the past 3 months. Main Outcomes and Measures: Semen quality, measured as volume, concentration, total sperm count, percentage of morphologically normal spermatozoa, and motility, and serum reproductive hormone levels, measured as follicle-stimulating hormone, luteinizing hormone, testosterone, free testosterone, and inhibin B levels. Results: Among 1679 young Danish men (median [interquartile range] age, 18.9 [18.7-19.4] years) recruited to participate, 98 men (5.8%) reported use of fish oil supplements during the past 3 months, of whom 53 (54.1%) reported intake on 60 or more days. After adjustment and compared with men with no supplement intake, men with fish oil supplement intake on fewer than 60 days had semen volume that was 0.38 (95% CI, -0.03 to 0.80) mL higher, and men with fish oil supplement intake on 60 or more days had semen volume that was 0.64 (95% CI, 0.15 to 1.12) mL higher (P for trend < .001). Similarly, testicular size in men with supplement intake on fewer than 60 days was 0.8 (95% CI, -0.2 to 1.9) mL larger and in men with fish oil supplement intake on 60 or more days was 1.5 (95% CI, 0.2 to 2.8) mL larger compared with men with no supplement intake (P for trend = .007). After adjustment, men with

fish oil supplement intake had a 20% (95% CI, 9%-31%) lower follicle-stimulating hormone level and 16% (95% CI, 8%-24%) lower luteinizing hormone level compared with men with no supplement intake. There were no associations of intake of other supplements with measures of testicular function. Conclusions and Relevance: These findings suggest that intake of fish oil supplements was associated with better testicular function, which is less likely to be due to confounding by indication, as no associations of intake of other supplements with testicular function were found. This cross-sectional study did not examine the actual content of omega-3 fatty acids in the supplements; therefore, these findings need confirmation in well-designed randomized clinical trials among unselected men.

[29] *Salas-Huetos A*. **More Evidence of the Association of Diet With Human Testicular Function-Fish Oil Supplements**. JAMA network open 2020; 3:e1919569.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31951268
ABSTRACT

[30] *Heng WK, Ng YP, Ooi GS et al.* **Comparison of the efficacy and level of adherence for morning versus evening versus before bedtime administration of simvastatin in hypercholesterolemic patients**. The Medical journal of Malaysia 2019; 74:477-482.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31929472
ABSTRACT
BACKGROUND: Simvastatin is usually taken in the evening due to the circadian rhythm of hepatic cholesterol biosynthesis. The degree of reduction of low-density lipoprotein cholesterol (LDL-C) and the level of adherence to different administration time remained unknown in the Malaysian population. This study aims to investigate the effect of simvastatin on the percentage changes of lipid profile and the level of adherence to when simvastatin was instructed to be taken at different timing. METHODS: Nine primary care health clinics across Malaysia participated in this study. 147 statin-naive subjects were selected through convenient sampling and randomised into one of the three arms (after breakfast, after dinner or before bedtime). Differences on percentage reduction of LDL-C from baseline and level of adherence among the three groups at week-16 were compared. The main outcomes measured in this study were the percentage change of lipid parameters and the percentage of high-adherence (MMAS=8) at week-16. RESULTS: 59.2% of the patients were male. The mean age of the study population was 53.93+/- 10.85 years. Most of the patients were Malays (69.4%); followed by Indians (22.4%) and Chinese (8.2%). LDL-C decreased from 4.26 (Standard Deviation, SD1.01) to 2.36 (SD0.69)mmol/L at week-16 for patients taking simvastatin before bedtime; an absolute reduction of 44.95%.The differences of LDL-C percentage reduction between three arms were significantly different ($p<0.001$). The greatest LDL-C reduction was observed when simvastatin was taken before bedtime and revealed 56.2% patients with high-adherence at week-16. CONCLUSION: Simvastatin showed superior LDL-reduction and higher level of adherence when being instructed to be taken before bedtime.

[31] *Swirski FK*. **Platelets have a dangerous hold over immune cells in cardiovascular disease**. Nature 2020; 577:323-324.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31937950
ABSTRACT

[32] *Vazquez-Borrego MC, Fuentes-Fayos AC, Herrera-Martinez AD et al.* **Statins directly regulate pituitary cell function and exert antitumor effects in pituitary tumors**. Neuroendocrinology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31940630

ABSTRACT

INTRODUCTION: Pituitary neuroendocrine tumors (PitNETs), the most abundant of all intracranial tumors, entail severe comorbidities. First-line therapy is transsphenoidal surgery, but subsequent pharmacological therapy is often required. Unfortunately, many patients are/become unresponsive to available drugs [somatostatin analogues (SSAs)/dopamine agonists], underscoring the need for new therapies. Statins are well-known drugs commonly prescribed to treat hyperlipidemia/cardiovascular diseases, but can convey additional beneficial effects, including antitumor actions. The direct effects of statins on normal human pituitary or PitNETs are poorly known. Thus, we aimed to explore the direct effects of statins, especially simvastatin, on key functional parameters in normal and tumoral pituitary cells, and to evaluate the combined effects of simvastatin with metformin or SSAs. METHODS: Effects of statins in cell proliferation/viability, hormone secretion, and signaling pathways were evaluated in normal pituitary cells from a primate model (Papio anubis), tumor cells from corticotropinomas, somatotropinomas, non-functioning pituitary-tumors (NFPTs), and PitNET cell-lines (AtT20/GH3-cells). RESULTS: All statins decreased AtT20-cell proliferation, simvastatin showing stronger effects. Indeed, simvastatin reduced cell viability and/or hormone secretion in all PitNETs subtypes and cell-lines, and ACTH/GH/PRL/FSH/LH secretion (but not expression), in primate cell cultures, by modulating MAPK/PI3K/mTOR pathways and expression of key receptors (GHRH-R/ghrelin-R/Kiss1-R) regulating pituitary function. Addition of MF or SSAs did not enhance simvastatin antitumor effects. CONCLUSION: Our data reveal direct antitumor effects of simvastatin on PitNET-cells, paving the way to explore these compounds as a possible tool to treat PitNETs.

[33] *He C, Xia P, Xu J et al.* **Evaluation of the efficacy of atorvastatin in the treatment for chronic subdural hematoma: a meta-analysis**. Neurosurgical review 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31953781

ABSTRACT

Atorvastatin therapy in chronic subdural hematoma patients has attracted more and more clinical attention. To evaluate the efficacy of atorvastatin in the treatment of chronic subdural hematoma. A systematic literature search was performed in the PubMed, Embase, and Cochrane Library databases; related controlled trials comparing the efficacy of atorvastatin in the treatment of chronic subdural hematoma published from inception to December 2018 were collected. We used Cochrane risk of bias method to evaluate the quality of the included studies. Meta-analysis was used to analyze the included data by RevMan 5.3 software. Of the 53 retrieved studies, 6 trials were included. Results of meta-analysis showed that compared with chronic subdural hematoma patients without atorvastatin treatment, both in patients who have had surgery and those who have not, atorvastatin were effective in reducing the incidence of recurrence requires surgery (OR = 0.30, 95% CI 0.19-0.48, P < 0.00001). And improve the recovery rate of neurological function of patients (OR = 1.75, 95% CI 1.08-2.83, P = 0.02). This meta-analysis suggests that patients with chronic subdural hematoma can improve their prognosis after receiving atorvastatin. Additionally, the neurological function recovery appears to be improving by atorvastatin.

[34] *Watts JK, Ockene IS*. **RNA Interference for the Masses? siRNA Targeting PCSK9 Promises Prevention of Cardiovascular Disease**. Nucleic acid therapeutics 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31928497
ABSTRACT

[35] *Genua I, Ramos A, Caimari F et al.* **Effects of Bariatric Surgery on HDL Cholesterol**. Obesity surgery 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31942689
ABSTRACT
BACKGROUND: Low levels of high-density lipoprotein cholesterol (HDLc) are independent predictive factors of coronary heart disease. Bariatric surgery increases HDLc concentration, but the chronology and predictors of this improvement in HDLc levels are not well-established. The aim of the present study was to analyse the changes over time in HDLc concentrations after bariatric surgery and to determine the predictors of their increase. SUBJECTS AND METHODS: This was a retrospective, observational study. The medical records of patients who had undergone bariatric surgery at a tertiary care hospital between January 2007 and March 2015 were reviewed. Patients who underwent revisional surgery or were treated with fibrates were excluded from the analysis. RESULTS: A total of 185 patients were included in the study. Follow-up rates were as follows: 87% (year 2) and 28% (year 5). At postoperative month 3, HDLc levels decreased significantly versus baseline (- 11.1%; p = 0.000), at which point they began to rise, reaching their maximum level 2 years after bariatric surgery (26.2% increase from baseline; p = 0.000). The increase in HDLc concentration 2 years after surgery correlated with the preoperative HDLc level (r = - 0.292, p = 0.001), and it was greater in patients who underwent sleeve gastrectomy versus gastric bypass (0.36 +/- 0.4 vs. 0.18 +/- 0.4 mmol/L, respectively; p = 0.018). CONCLUSION: Bariatric surgery has a beneficial effect on HDLc levels. The maximum increase in postoperative HDLc concentrations is observed 2 years after surgery. Preoperative HDLc and the type of surgery are both significant predictors of the maximum increase in HDLc levels.

[36] *Tavakkoli A, Johnston TP, Sahebkar A*. **Antifungal effects of statins**. Pharmacology & therapeutics 2020:107483.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31953128
ABSTRACT
Fungal infections are estimated to be responsible for 1.5 million deaths annually. Global anti-microbial resistance is also observed for fungal pathogens, and scientists are looking for new antifungal agents to address this challenge. One potential strategy is to evaluate currently available drugs for their possible antifungal activity. One of the suggested drug classes are statins, which are commonly used to decrease plasma cholesterol and reduce cardiovascular risk associated with low density lipoprotein cholesterol (LDL-c). Statins are postulated to possess pleiotropic effects beyond cholesterol lowering; improving endothelial function, modulating inflammation, and potentially exerting anti-microbial effects. In this study, we reviewed in-vitro and in-vivo studies, as well as clinical reports pertaining to the antifungal efficacy of statins. In addition, we have addressed various modulators of statin anti-fungal activity and the potential mechanisms responsible for their anti-fungal effects. In general, statins do possess anti-fungal activity, targeting a broad spectrum of

fungal organisms including human opportunistic pathogens such as Candida spp. and Zygomycetes, Dermatophytes, alimentary toxigenic species such as Aspergillus spp., and fungi found in device implants such as Saccharomyces cerevisiae. Statins have been shown to augment a number of antifungal drug classes, for example, the azoles and polyenes. Synthetic statins are generally considered more potent than the first generation of fungal metabolites. Fluvastatin is considered the most effective statin with the broadest and most potent fungal inhibitory activity, including fungicidal and/or fungistatic properties. This has been demonstrated with plasma concentrations that can easily be achieved in a clinical setting. Additionally, statins can potentiate the efficacy of available antifungal drugs in a synergistic fashion. Although only a limited number of animal and human studies have been reported to date, observational cohort studies have confirmed that patients using statins have a reduced risk of candidemia-related complications. Further studies are warranted to confirm our findings and expand current knowledge of the anti-fungal effects of statins.

[37] *Kuzma L, Bachorzewska-Gajewska H, Kozuch M et al.* **Acute coronary syndromes and atherosclerotic plaque burden distribution in coronary arteries among patients with valvular heart disease (BIA-WAD registry)**. Postepy w kardiologii interwencyjnej = Advances in interventional cardiology 2019; 15:422-430.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31933658
ABSTRACT
Introduction: Valvular heart diseases (VHD) are a significant problem in the Polish population. Coexistence of coronary artery disease (CAD) in patients with VHD increases the risk of death and affects the further therapeutic strategy. Aim: Analysis of atherosclerotic plaque burden distribution in coronary arteries and long-term prognosis among patients with VHD. Material and methods: Inclusion criteria were met by 1025 patients with moderate and severe VHD. Mean observation time was 2528 +/-1454 days. Results: Severe aortic valve stenosis (AVS) occurred in 28.2%, severe mitral valve insufficiency (MVI) in 20%. CAD with severe angiographic stenoses was noted in 42.3% (n = 434). Among patients with severe MVI, CAD was noted in 47.1% of cases, and prior acute coronary syndromes (ACS) in 27.1% of patients (n = 58). In severe AVS patients, significant angiographic atherosclerotic changes were observed in 29.6% (n = 86), and prior ACS in 7.6% (n = 22) of patients. During the observation 52.7% of patients died, including 62.9% of patients with severe MVI and 51.6% of those with severe AVS. Age (OR = 1.038; 95% CI: 1.005-1.072; p = 0.022) and coexisting aortic valve insufficiency (AVI) (OR = 2.39, 95% CI: 5.370-11.065, p = 0.035) increased the mortality rate. Conclusions: Severe AVS is starting to be the most prevalent VHD. CAD is one of the most significant factors deteriorating prognosis of patients with VHD. AVI and age were significant risk factors for mortality. The worst prognosis was observed in severe MVI, which may result from more frequent occurrence of CAD in this group. A lesser burden of CAD and ACS in the group of patients with severe AVS did not affect survival.

[38] *McDaniel JC, Rausch J, Tan A*. **Impact of omega-3 fatty acid oral therapy on healing of chronic venous leg ulcers in older adults: Study protocol for a randomized controlled single-center trial**. Trials 2020; 21:93.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31948466
ABSTRACT

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BACKGROUND: This trial addresses the global problem of chronic venous leg ulcers (CVLUs), wounds that cause significant infirmity for an estimated 9.7 million people annually, mainly older adults with comorbidities. Advanced therapies are needed because standard topical therapies are often ineffective or yield only short-term wound healing. Thus, we are testing a new oral therapy containing the bioactive elements of fish oil, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), for targeting and reducing the high numbers of activated polymorphonuclear leukocytes (PMN) in wound microenvironments that keep CVLUs "trapped" in a chronic inflammatory state. METHODS: This double-blind RCT will include 248 eligible adults >/= 55 years of age with CVLUs receiving standard care at a large Midwest outpatient wound clinic. Participants are randomized to two groups: 12 weeks of daily oral therapy with EPA + DHA (1.87 g/day of EPA + 1.0 g/day of DHA) or daily oral therapy with placebo. At 0, 4, 8, and 12 weeks, across the two groups, we are pursuing three specific aims: Aim 1. Compare levels of EPA + DHA-derived lipid mediators, and inflammatory cytokines in blood and wound fluid; Subaim 1a. Compare inflammatory cytokine gene expression by PMNs in blood; Aim 2. Compare PMN activation in blood and wound fluid, and PMN-derived protease levels in wound fluid; Aim 3. Compare reduction in wound area, controlling for factors known to impact healing, and determine relationships with lipid mediators, cytokines, and PMN activation. Subaim 3a. Compare frequency of CVLU recurrence and levels of study variables in blood between the randomly assigned two subgroups (continuing EPA + DHA therapy versus placebo therapy beyond week 12) within the EPA + DHA group with healed CVLUs after 3 months of therapy. Subaim 3b. Compare symptoms of pain at all time points and quality of life at first and last time points across the two groups and two subgroups. DISCUSSION: This trial will provide new evidence about the effectiveness of EPA + DHA oral therapy to target and reduce excessive PMN activation systemically and locally in patients with CVLUs. If effective, this therapy may facilitate healing and thus be a new adjunct treatment for CVLUs in the aging population. TRIAL REGISTRATION: ClinicalTrials.gov, NCT03576989; Registered on 13 June 2018.