[1] *Mitaritonno M, Lupo M, Greco I et al.* **Severe rhabdomyolysis induced by co-administration of cocaine and heroin in a 45 years old man treated with rosuvastatin: a case report**. Acta biomedica : Atenei Parmensis 2021; 92:e2021089.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33944852

ABSTRACT

The term rhabdomyolysis describes a damage involving striated muscle cells or fibers, often complicated by acute kidney injury. This syndrome can have different causes, but it is generally divided into two main categories: traumatic and non-traumatic rhabdomyolysis. Among medical causes, drugs and abuse substances play a pivotal role, being opioids, alcohol, cocaine and other substances of abuse. Among drugs, the case of statins is certainly the best known. Here we describe a paradigmatic case of a man treated with success and good tolerance for years with rosuvastatin, who developed a severe rhabdomyolysis complicated by AKI needing hemodialysis, after the assumption of two substances of abuse (cocaine and heroin). Emergency physicians need to be aware of this syndrome, since it must be clinically suspected in order to ask the Laboratory for appropriate tests. Given that troponins are now widely accepted as the unique biochemical "gold standard" for diagnosing acute coronary syndromes, CK and myoglobin (the "gold standard" tests for diagnosing rhabdomyolysis) have been erased from admission test panels of the vast majority of emergency departments.

[2] *Zanchin C, Koskinas KC, Ueki Y et al.* **Effects of the PCSK9 antibody alirocumab on coronary atherosclerosis in patients with acute myocardial infarction: a serial, multivessel, intravascular ultrasound, near-infrared spectroscopy and optical coherence tomography imaging study-Rationale and design of the PACMAN-AMI trial**. American heart journal 2021; 238:33-44.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33951415

ABSTRACT

BACKGROUND: The risk for cardiovascular adverse events after acute myocardial infarction (AMI) remains high despite potent medical treatment including low-density lipoprotein cholesterol (LDL-C) lowering with statins. Proprotein convertase subtilisin/kexin type 9 (PCSK9) antibodies substantially reduce LDL-C when added to statin. Alirocumab, a monoclonal antibody to PCSK9, reduces major adverse cardiovascular events after AMI. The effects of alirocumab on coronary atherosclerosis including plaque burden, plaque composition and fibrous cap thickness in patients presenting with AMI remains unknown. AIMS: To determine the effect of LDL-C lowering with alirocumab on top of high-intensity statin therapy on intravascular ultrasound (IVUS)-derived percent atheroma volume (PAV), near-infrared spectroscopy (NIRS)-derived maximum lipid core burden index within 4 mm (maxLCBI(4 mm)) and optical coherence tomography (OCT)-derived fibrous cap thickness (FCT) in patients with AMI. METHODS: In this multicenter, double-blind, placebo-controlled trial, 300 patients with AMI (ST-elevation or non-ST-elevation myocardial infarction) were randomly assigned to receive either biweekly subcutaneous alirocumab (150 mg) or placebo beginning <24 hours after the acute event as add-on therapy to rosuvastatin 20 mg. Patients undergo serial IVUS, NIRS and OCT in the two non-infarct related arteries at baseline (at the time of treatment of the culprit lesion) and at 52 weeks. The primary endpoint, change in IVUS-derived PAV, and the powered secondary endpoints, change in NIRS-derived maxLCBI(4 mm), and OCT-derived minimal FCT, will be assessed 52 weeks post randomization. SUMMARY: The PACMAN-AMI trial will determine the effect of alirocumab on

top of high-intensity statin therapy on high-risk coronary plaque characteristics as assessed by serial, multimodality intracoronary imaging in patients presenting with AMI. CLINICAL TRIAL REGISTRATION: NCT03067844.

[3] *Hardy J, Niman S, Pereira E et al.* **A Critical Review of the Efficacy and Safety of Inclisiran**. American journal of cardiovascular drugs : drugs, devices, and other interventions 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33954930

ABSTRACT

The association between low-density cholesterol (LDL-C) and cardiovascular disease (CVD) is well-established, with an emphasis on lowering LDL-C levels to reduce cardiovascular events. Statin therapy has been the traditional treatment for LDL-C reduction, in addition to lifestyle modifications, but studies have shown that a substantial proportion of patients does not reach target LDL-C goals despite receiving maximally tolerated statin medications. Additionally, statin therapy is associated with a few shortcomings as many patients initiated on these medications discontinue treatment within 1 year because of lack of tolerability. Furthermore, guidelines from both the American College of Cardiology and the American Heart Association highlight the importance of obtaining LDL-C goals because of the residual atherosclerotic CVD risk that remains in high-risk populations. That the residual cardiovascular risk remains despite statin therapy highlights the importance of evaluating therapeutic approaches that possess effective lipid lowering that can be used adjunctively with statins. Much focus has been directed towards the proprotein convertase subtilisin/kexin type 9 (PCSK9) pathway, leading to the development of evolocumab and alirocumab, two human monoclonal antibodies directed against PCSK9. These agents have been shown to markedly decrease LDL-C levels and significantly reduce cardiovascular risk, but the need for biweekly or monthly subcutaneous injections has generated concerns for patient compliance. A new pathway is being studied in which a synthetic small interfering ribonucleic acid (siRNA) targets the PCSK9 gene expressed in hepatocytes to prevent PCSK9 production. The siRNA, inclisiran sodium, significantly reduces hepatic production of PCSK9, causing a marked reduction in LDL-C levels, and exhibits sustained pharmacodynamic effects when dosed subcutaneously every 6 months. This review presents and discusses the current clinical and scientific evidence pertaining to inclisiran sodium.

[4] *Zhou K, Qin Z, Tian J et al.* **The Atherogenic Index of Plasma: A Powerful and Reliable Predictor for Coronary Artery Disease in Patients With Type 2 Diabetes**. Angiology 2021:33197211012129.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33949211

ABSTRACT

We evaluated the predictive power of the atherogenic index of plasma (AIP) for coronary artery disease (CAD) in patients with type 2 diabetes mellitus (T2DM). A total of 3278 patients who underwent coronary angiography were consecutively enrolled, including 2052 patients with CAD and 1226 patients with T2DM but without CAD. Patients in the CAD group had higher levels of triglyceride (TG), total cholesterol, low-density lipoprotein cholesterol, AIP and a lower level of high-density lipoprotein cholesterol (HDL-C). In correlation analyses, AIP correlated positively with body mass index, log (homeostasis model assessment of insulin resistance), TG, remnant lipoprotein cholesterol, non-HDL-C, but negatively with age and HDL-C. Multivariate logistic regression analyses demonstrated that AIP was an independent risk factor for CAD in diabetic patients and was validated

by multiple models. Furthermore, the ORs for CAD risk were raised with increasing AIP quartiles; ORs of AIP quartiles Q2-Q4 compared with Q1 were 1.56, 1.70, and 2.22, respectively (Ps < .001), which suggested AIP was the lipid parameter that most strongly associated with incident CAD. In conclusion, AIP is a powerful and reliable biomarker for predicting CAD risk beyond individual lipid profiles in patients with T2DM.

[5] *Rumora AE, Guo K, Alakwaa FM et al.* **Plasma lipid metabolites associate with diabetic polyneuropathy in a cohort with type 2 diabetes**. Annals of clinical and translational neurology 2021; 8:1292-1307.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33955722

ABSTRACT

OBJECTIVE: The global rise in type 2 diabetes is associated with a concomitant increase in diabetic complications. Diabetic polyneuropathy is the most frequent type 2 diabetes complication and is associated with poor outcomes. The metabolic syndrome has emerged as a major risk factor for diabetic polyneuropathy; however, the metabolites associated with the metabolic syndrome that correlate with diabetic polyneuropathy are unknown. METHODS: We conducted a global metabolomics analysis on plasma samples from a subcohort of participants from the Danish arm of Anglo-Danish-Dutch study of Intensive Treatment of Diabetes in Primary Care (ADDITION-Denmark) with and without diabetic polyneuropathy versus lean control participants. RESULTS: Compared to lean controls, type 2 diabetes participants had significantly higher HbA1c ($p = 0.0028$), BMI ($p = 0.0004$), and waist circumference ($p = 0.0001$), but lower total cholesterol ($p = 0.0001$). Out of 991 total metabolites, we identified 15 plasma metabolites that differed in type 2 diabetes participants by diabetic polyneuropathy status, including metabolites belonging to energy, lipid, and xenobiotic pathways, among others. Additionally, these metabolites correlated with alterations in plasma lipid metabolites in type 2 diabetes participants based on neuropathy status. Further evaluating all plasma lipid metabolites identified a shift in abundance, chain length, and saturation of free fatty acids in type 2 diabetes participants. Importantly, the presence of diabetic polyneuropathy impacted the abundance of plasma complex lipids, including acylcarnitines and sphingolipids. INTERPRETATION: Our explorative study suggests that diabetic polyneuropathy in type 2 diabetes is associated with novel alterations in plasma metabolites related to lipid metabolism.

[6] *Sucharitkul PPJ, Jones KL, Scott DJA, Bailey MA.* **Lipid Optimization in Lower Extremity Peripheral Arterial Disease**. Annals of vascular surgery 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33951531

ABSTRACT

AIMS: This review aims to explore the current guidance and issues surrounding lipid optimisation of patients with peripheral arterial disease (PAD). METHODS: A narrative review of the global PAD guidance, specifically focusing on low density lipoprotein cholesterol (LDL-C) reduction methods including; 'treating to target', 'fire and forget' and LDL-C percentage reduction. Advanced literature searches were carried out in Pubmed and Google Scholar databases comparing most recent PAD lipid guidance. RESULTS: PAD lipid guidance could be improved internationally to help clinicians implement the best lipid-reduction strategies for their patients and challenge the arbitrary 1.4 mmol/L LDL-C target in line with novel proprotein convertase subtilisin/kexin type 9 inhibitors trials. By educating primary and secondary care staff on the benefits of maximal lipid-reduction therapies, we

can reduce major adverse cardiovascular events and major adverse limb events. Championing PAD community clinics may lead to earlier prevention. Research comparing lipid-reduction strategies in practice is needed to improve outcomes internationally, and ongoing practice audited to understand the extent of under-prescribing in PAD. CONCLUSIONS: This review highlights the current PAD lipid-reduction treatments and the clarity issues of global guidance. Further research is needed to tackle ongoing mortality and morbidity rates in PAD patients against their better off cardiovascular disease (CVD) peers. MESH KEY TERMS: "Cholesterol", "Hydroxymethylglutaryl-CoA Reductase Inhibitors", "Ezetimibe", "Evolocumab", "Alirocumab", "Peripheral Arterial Disease", "Vascular Disease", "Atherosclerosis", "Secondary Prevention", "Lipoprotein, LDL".

[7] *K BU, Benito-Vicente A, Martin C et al.* **(r)HDL in theranostics: how do we apply HDL's biology for precision medicine in atherosclerosis management?** Biomater Sci 2021; 9:3185-3208.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33949389

ABSTRACT

High-density lipoproteins (HDL) are key players in cholesterol metabolism homeostasis since they are responsible for transporting excess cholesterol from peripheral tissues to the liver. Imbalance in this process, due to either excessive accumulation or impaired clearance, results in net cholesterol accumulation and increases the risk of cardiovascular disease (CVD). Therefore, significant effort has been focused on the development of therapeutic tools capable of either directly or indirectly enhancing HDL-guided reverse cholesterol transport (RCT). More recently, in light of the emergence of precision nanomedicine, there has been renewed research interest in attempting to take advantage of the development of advanced recombinant HDL (rHDL) for both therapeutic and diagnostic purposes. In this review, we provide an update on the different approaches that have been developed using rHDL, focusing on the rHDL production methodology and rHDL applications in theranostics. We also compile a series of examples highlighting potential future perspectives in the field.

[8] *Lee S, Zhou J, Wong WT et al.* **Glycemic and lipid variability for predicting complications and mortality in diabetes mellitus using machine learning**. BMC endocrine disorders 2021; 21:94.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33947391

ABSTRACT

INTRODUCTION: Recent studies have reported that HbA1c and lipid variability is useful for risk stratification in diabetes mellitus. The present study evaluated the predictive value of the baseline, subsequent mean of at least three measurements and variability of HbA1c and lipids for adverse outcomes. METHODS: This retrospective cohort study consists of type 1 and type 2 diabetic patients who were prescribed insulin at outpatient clinics of Hong Kong public hospitals, from 1st January to 31st December 2009. Standard deviation (SD) and coefficient of variation were used to measure the variability of HbA1c, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglyceride. The primary outcome is all-cause mortality. Secondary outcomes were diabetes-related complications. RESULT: The study consists of 25,186 patients (mean age = 63.0, interquartile range [IQR] of age = 15.1 years, male = 50%). HbA1c and lipid value and variability were significant predictors of all-cause mortality. Higher HbA1c and lipid variability measures were associated with increased risks of neurological, ophthalmological and renal complications, as well as incident dementia, osteoporosis, peripheral vascular disease, ischemic heart disease, atrial fibrillation and heart failure ($p < 0.05$). Significant association was found between

hypoglycemic frequency (p< 0.0001), HbA1c (p< 0.0001) and lipid variability against baseline neutrophil-lymphocyte ratio (NLR). CONCLUSION: Raised variability in HbA1c and lipid parameters are associated with an elevated risk in both diabetic complications and all-cause mortality. The association between hypoglycemic frequency, baseline NLR, and both HbA1c and lipid variability implicate a role for inflammation in mediating adverse outcomes in diabetes, but this should be explored further in future studies.

[9] *Nasir K, Cainzos-Achirica M*. **Role of coronary artery calcium score in the primary prevention of cardiovascular disease**. Bmj 2021; 373:n776.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33947652
ABSTRACT
First developed in 1990, the Agatston coronary artery calcium (CAC) score is an international guideline-endorsed decision aid for further risk assessment and personalized management in the primary prevention of atherosclerotic cardiovascular disease. This review discusses key international studies that have informed this 30 year journey, from an initial coronary plaque screening paradigm to its current role informing personalized shared decision making. Special attention is paid to the prognostic value of a CAC score of zero (the so called "power of zero"), which, in a context of low estimated risk thresholds for the consideration of preventive therapy with statins in current guidelines, may be used to de-risk individuals and thereby inform the safe delay or avoidance of certain preventive therapies. We also evaluate current recommendations for CAC scoring in clinical practice guidelines around the world, and past and prevailing barriers for its use in routine patient care. Finally, we discuss emerging approaches in this field, with a focus on the potential role of CAC informing not only the personalized allocation of statins and aspirin in the general population, but also of other risk-reduction therapies in special populations, such as individuals with diabetes and people with severe hypercholesterolemia.

[10] *Lorenzatti AJ, Monsalvo ML, López JAG et al.* **Effects of evolocumab in individuals with type 2 diabetes with and without atherogenic dyslipidemia: An analysis from BANTING and BERSON**. Cardiovascular diabetology 2021; 20:94.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33941192
ABSTRACT
BACKGROUND: Atherogenic dyslipidemia (AD), characterized by increased concentrations of apolipoprotein B (ApoB)-containing particles, is often present in individuals with type 2 diabetes mellitus (T2DM). Non-high-density lipoprotein cholesterol (non-HDL-C), cholesterol transported by apolipoprotein B (ApoB)-containing particles), and total apoB are considered secondary goals of lipid-lowering therapy to guide treatment of residual cardiovascular risk. The BANTING and BERSON studies demonstrated that evolocumab added to statin therapy reduced atherogenic lipid and lipoproteins concentrations in patients with T2DM. METHODS: This post-hoc analysis combined data from two randomized, placebo-controlled trials, BANTING and BERSON, to investigate the effect of evolocumab (140 mg every two weeks [Q2W] or 420 mg monthly [QM]) on atherogenic lipid (LDL-C, non-HDL-C, VLDL-C, remnant cholesterol) and lipoproteins (ApoB, lipoprotein(a) (Lp[a])), and achievement of 2019 European Society of Cardiology/European Atherosclerosis Society lipid treatment goals in individuals with and without AD. RESULTS: In individuals with high TGs with (n = 389) and without (n = 196) AD receiving background statin therapy, evolocumab, compared with

placebo, substantially reduced the cholesterol levels from all ApoB atherogenic lipoproteins (least squares (LS) mean LDL-C by 66.7% to 74.3%, non-HDL-C by 53.4% to 65.8%, median remnant cholesterol by 28.9% to 34.2%, VLDL-C by 16.1% to 19.6%) and median TGs levels (by 17.5% to 19.6%) at the mean of weeks 10 and 12. LS mean ApoB was significantly reduced by 41.5% to 56.6% at week 12. Results were consistent in diabetic individuals with normal TGs (n=519). Evolocumab was also associated with a significant reduction in median Lp(a) by 35.0% to 53.9% at the mean of weeks 10 and 12. A majority (74.7% to 79.8%) of evolocumab-treated individuals achieved the goal of both an LDL-C<1.4 mmol/L and an LDL-C reduction of at least 50%,>75% achieved non-HDL-C<2.2 mmol/L at the mean of weeks 10 and 12, and>67% achieved ApoB<65 mg/dL at week 12. CONCLUSIONS: Evolocumab effectively reduced LDL-C, non-HDL-C, ApoB, Lp(a), and remnant cholesterol in individuals with T2DM with and without AD. Evolocumab Q2W or QM enabled most individuals at high/very-high cardiovascular disease risk to achieve their LDL-C, non-HDL-C, and ApoB recommended goals.

[11] *Servadei F, Anemona L, Cardellini M et al.* **The risk of carotid plaque instability in patients with metabolic syndrome is higher in women with hypertriglyceridemia**. Cardiovascular diabetology 2021; 20:98.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33957931
ABSTRACT
BACKGROUND: Metabolic syndrome certainly favors growth of carotid plaque; however, it is uncertain if it determines plaque destabilization. Furthermore, it is likely that only some components of metabolic syndrome are associated with increased risk of plaque destabilization. Therefore, we evaluated the effect of different elements of metabolic syndrome, individually and in association, on carotid plaques destabilization. METHODS: A total of 186 carotid endarterectomies from symptomatic and asymptomatic patients were histologically analysed and correlated with major cardiovascular risk factors. RESULTS: Metabolic syndrome, regardless of the cluster of its components, is not associated with a significant increase in risk of plaque destabilization, rather with the presence of stable plaques. The incidence of unstable plaques in patients with metabolic syndrome is quite low (43.9%), when compared with that seen in the presence of some risk factors, but significantly increases in the subgroup of female patients with hypertriglyceridemia, showing an odds ratio of 3.01 (95% CI, 0.25-36.30). CONCLUSIONS: Our data may help to identify patients with real increased risk of acute cerebrovascular diseases thus supporting the hypothesis that the control of hypertriglyceridemia should be a key point on prevention of carotid atherosclerotic plaque destabilization, especially in post-menopausal female patients.

[12] *Inoue K, Figueroa JF, DeJong C et al.* **Association Between Industry Marketing Payments and Prescriptions for PCSK9 (Proprotein Convertase Subtilisin/Kexin Type 9) Inhibitors in the United States**. Circulation. Cardiovascular quality and outcomes 2021; 14:e007521.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33966446
ABSTRACT
BACKGROUND: Marketing payments from the pharmaceutical industry to physicians have come under scrutiny due to their potential to influence clinical decision-making. Two proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) were approved by the US Food and Drug Administration in 2015 for reducing low-density lipoprotein cholesterol in high-risk patients, but their initial uptake was

limited due to their high-cost and stringent prior authorization requirements. We sought to investigate the association between industry marketing and early adoption of PCSK9i among US physicians. METHODS: We used nationwide databases of primary care physicians, cardiologists, and endocrinologists treating Medicare beneficiaries to examine the association between PCSK9i-related marketing payments in 2016 and the number of filled PCSK9i prescriptions in 2017, after adjusting for physician characteristics. In subgroup analyses, we stratified our analyses by physician specialty and prior experience with prescribing PCSK9i. RESULTS: Among 209 840 physicians included in this analysis, 49 341 (24%) physicians received 292 941 PCSK9i-related marketing payments in 2016. The total value of these payments was $19 million, with a median payment of $61 per physician (interquartile range, $25-$132). Most payments (95%) were for meals, with a median of $14 per meal. The receipt of PCSK9i-related payments in 2016 was associated with increased PCSK9i prescription in 2017 (adjusted risk ratio, 3.18 [95% CI, 2.95-3.42]). This association was larger among primary care physicians (adjusted risk ratio, 6.67 [95% CI, 5.87-7.57]) than cardiologists (adjusted risk ratio, 2.00 [95% CI, 1.84-2.16]) and endocrinologists (adjusted risk ratio, 4.06 [95% CI, 2.95-5.59]). The association was observed across all types of payments. CONCLUSIONS: At a time when few physicians had experience with prescribing PCSK9i under strict prior authorization requirements, industry marketing payments to physicians for PCSK9i, predominantly in the form of meals, were associated with increased PCSK9i prescription in the subsequent year.

[13] *Ikari Y, Matsue Y, Torii S et al.* **Association Between Statin Use Prior to Admission and Lower Coronavirus Disease 2019 (COVID-19) Severity in Patients With Cardiovascular Disease or Risk Factors**. Circulation journal : official journal of the Japanese Circulation Society 2021; 85:939-943.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33952833
ABSTRACT
BACKGROUND: Cardiovascular diseases and/or risk factors (CVDRF) have been reported as risk factors for severe coronavirus disease 2019 (COVID-19).Methods and Results:In total, we selected 693 patients with CVDRF from the CLAVIS-COVID database of 1,518 cases in Japan. The mean age was 68 years (35% females). Statin use was reported by 31% patients at admission. Statin users exhibited lower incidence of extracorporeal membrane oxygenation (ECMO) insertion (1.4% vs. 4.6%, odds ratio [OR]: 0.295, P=0.037) and septic shock (1.4% vs. 6.5%, OR: 0.205, P=0.004) despite having more comorbidities such as diabetes mellitus. CONCLUSIONS: This study suggests the potential benefits of statins use against COVID-19.

[14] *Chakraborty A, Pang J, Chan DC et al.* **Effectiveness of proprotein convertase subtilisin/kexin-9 monoclonal antibody treatment on plasma lipoprotein(a) concentrations in patients with elevated lipoprotein(a) attending a clinic**. Clinical cardiology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33955565
ABSTRACT
BACKGROUND: Lipoprotein(a) (Lp[a]) is a causal risk factor for atherosclerotic cardiovascular disease (ASCVD). Proprotein convertase subtilisin/kexin-9 monoclonal antibodies (PCSK9mAbs) can lower Lp(a) levels in clinical trials, but their effects in patients with elevated Lp(a) in clinical practice remain unclear. AIMS: To investigate the effectiveness and safety of PCSK9mAbs in lowering plasma Lp(a) in patients with elevated Lp(a) concentrations in a lipid clinic. METHODS: This was an open-

label study of 53 adult patients with elevated Lp(a) concentration (≥0.5 g/L). Clinical, biochemical, and safety data were collected before and on treatment with evolocumab or alirocumab over a mean period of 11 months. RESULTS: Treatment with a PCSK9mAb resulted in a significant reduction of 0.29 g/L (-22%) in plasma Lp(a) concentration (p<.001). There were also significant reductions in low-density lipoprotein-cholesterol (LDL-C) (-53%), remnant-cholesterol (-12%) and apolipoprotein B (-43%) concentrations. The change in Lp(a) concentration was significantly different from a comparable group of 35 patients with elevated Lp(a) who were not treated with a PCSK9mAb (-22% vs. -2%, p<.001). The reduction in Lp(a) concentration was not associated with the corresponding changes in LDL-C, remnant-cholesterol, and apolipoprotein B (p>.05 in all). 7.5% and 47% of the patients attained a target concentration of Lp(a) <0.5 g/L and LDL-C <1.8 mmol/L, respectively. PCSK9mAbs were well tolerated, the common adverse effects being pharyngitis (9.4%), nasal congestion (7.6%), myalgia (9.4%), diarrhoea (7.6%), arthralgia (9.4%) and injection site reactions (11%). CONCLUSION: PCSK9mAbs can effectively and safely lower plasma Lp(a) concentrations in patients with elevated Lp(a) in clinical practice; the impact of the fall in Lp(a) on ASCVD outcomes requires further investigation.

[15] *Ghodsi S, Mohebi M, Sadre-Bafghi SA et al.* **Prognostic implications of calculated Apo-lipoprotein B in patients with segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: Outcome is tied to lower cut-points**. Clinical cardiology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33942349
ABSTRACT
BACKGROUND: Debates still surround using lipoproteins including Apo-B in risk assessment, management, and prognosis of patients with coronary artery disease. During an acute ST-segment elevation myocardial infarction, Apo-B might help to achieve incremental prognostic information. OBJECTIVE: We sought to determine the potential prognostic utility of calculated Apo-B in a cohort of patients with STEMI undergoing primary PCI. METHODS: A retrospective cohort study was conducted enrolling 2,259 patients with a diagnosis of acute STEMI who underwent primary PCI. Apo-B was obtained using a valid equation based on initial lipid measurements. High Apo-B was defined as a level of 65 or higher. Primary endpoint of the study was major adverse cardiovascular events (MACE). RESULTS: Mean age of the participants was 59.54 years and 77.9% of them were male. After a Median follow up of 15 (6.2) months, high Apo-B was associated with MACE and the OR (95% CI) was 3.02 (1.07-8.47), p = .036. Odds ratios for prediction of MACE pertaining to LVEF, and smoking were 0.97 (p = .044), and 1.07 (p = .033), respectively. However, High Apo-B was not able to predict suboptimal TIMI flow. Accordingly, the Odds ratio was 0.56 (0.17-1.87), p = 0.349. The power of High LDL-C and Non-HDLC for prediction of MACE were assessed in distinct models. Attained odds ratios were [2.40 (0.90-6.36), p = .077] and [1.80 (0.75-4.35), p = 0.191], respectively. CONCLUSION: Calculated Apo-B appears to be a simple tool applicable for prediction of cardiovascular events in patients with STEMI superior to both Non-HDLC and LDL-C.

[16] *Guijarro C, Cosín-Sales J.* **LDL cholesterol and atherosclerosis: The evidence**. Clinica e investigacion en arteriosclerosis : publicacion oficial de la Sociedad Espanola de Arteriosclerosis 2021; 33 Suppl 1:25-32.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33966809

ABSTRACT
The lipid theory of atherosclerosis dates back more than a century. Despite this, some authors have questioned the relevance of hypercholesterolaemia in its development. Multiple experimental, epidemiological, and clinical evidence underpins this association. Atherosclerotic cardiovascular disease remains as the major cause of mortality in the world. Recent genetic studies of Mendelian randomisation and randomised clinical trials aimed at LDL cholesterol reduction, are summarised in this article. They, unequivocally ratify the aetiological role of LDL cholesterol in the development of atherosclerosis. Thus, LDL cholesterol lowering is the cornerstone of lipid lowering therapy for the reduction of cardiovascular complications of atherosclerosis.

[17] *Lekuona I, Pintó X*. **Clinical development of bempedoic acid: phase 2 and phase 3 clinical trials**. Clinica e investigacion en arteriosclerosis : publicacion oficial de la Sociedad Espanola de Arteriosclerosis 2021; 33 Suppl 1:58-64.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33966815
ABSTRACT
We review all the phase II and III studies carried out with bempedoic acid at the dose of 180mg, alone or in combination with different lipid-lowering drugs and in different subgroups of patients that unequivocally show the efficacy and safety of the drug. We point out some of the potential advantages of its use in clinical practice in patients with statin intolerance and the efficacy in reducing LDL-c when combined with statins, and with statins and ezetimibe, as well as in reducing inflammation markers pending the results of the CV Clear Outcomes trial that will end in 2022.

[18] *López-Miranda J, Pedro-Botet J*. **Therapeutic targets in the treatment of dyslipidaemias: From statins to PCSK9 inhibitors. Unmet needs**. Clinica e investigacion en arteriosclerosis : publicacion oficial de la Sociedad Espanola de Arteriosclerosis 2021; 33 Suppl 1:46-52.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33966813
ABSTRACT
The use of low-density lipoprotein cholesterol (LDLc)-lowering medications has led to a significant reduction of cardiovascular risk in both primary and secondary prevention. Statins represent the cornerstone of lipid-lowering treatment and substantially decreases cardiovascular morbidity and mortality. However, there are still unmet clinical needs in the management of dyslipidaemia. Indeed, it is difficult to achieve LDLc targets in many patients, particularly in those at high/very high cardiovascular risk and in those with very high baseline LDLc concentrations. Moreover, a considerable proportion of patients are unable to tolerate maximum statin doses, mostly due to muscle-related adverse effects. In the present narrative review, a summary is presented on the current knowledge on the effects of the different cholesterol-lowering drugs, including those recently approved by European and American regulatory agencies, on lipid profile, and on cardiovascular risk. Since difficult-to-treat patients may benefit from new combination therapies as a result of the emergence of new drugs with clinical evidence, updates of the clinical guidelines would be recommended.

[19] *Marco-Benedí V, Jarauta Simón E, Laclaustra Gimeno M, Civeira Murillo F*. **Nursing workload. Calculation of cardiovascular risk and therapeutic objectives**. Clinica e investigacion en

arteriosclerosis : publicacion oficial de la Sociedad Espanola de Arteriosclerosis 2021; 33 Suppl 1:10-17.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33966807
ABSTRACT
Therapeutic intervention should be determined by the risk of developing atheromatous cardiovascular disease (CVD). The higher the risk, the more intense the action should be. This is the reason for the stratification of patient risk. In primary prevention, the two main guidelines used, the American Heart Association and the American College of Cardiology (ACC/AHA) use the Pooled cohort equations (PCE) and the guidelines of the European societies use the SCORE tables. The PCE calculates the risk of fatal and non-fatal CVD, and the SCORE calculates risk of fatal CVD only. In young people, it is useful to consider the lifetime risk calculation. The Spanish Society of Arteriosclerosis (SEA) recommends the SCORE system in Spain. SCORE and PCE calculate the risk for people up to 70 and 75 years of age. Prediction and potentials are available for 80 years of age and above, with the data available being much more scarce. Risk stratification in secondary prevention may be useful to identify the subgroup of patients who may benefit from more intensive treatment. Imaging tests, especially coronary calcium scans and vascular ultrasound, can help to better the profile risk. European guidelines identify LDL cholesterol as a therapeutic target. They recommend initiating treatment with statins, and increasing dose and potency until targets are achieved, and then to treatment with potent statins at a maximum tolerated dose, and ezetimibe if targets are not achieved. As a third step, PCSK9 inhibitors are indicated. They set very ambitious targets, as low as 40 mg/dL in those subjects with recurrences before two years of CVD despite high-intensity statin therapy, and below 55 mg/dL for all very high-risk subjects.

[20] *Masana Marín L, Plana Gil N*. **Bempedoic acid. Mechanism of action and pharmacokinetic and pharmacodynamic properties**. Clinica e investigacion en arteriosclerosis : publicacion oficial de la Sociedad Espanola de Arteriosclerosis 2021; 33 Suppl 1:53-57.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33966814
ABSTRACT
Bempedoic acid acts by inhibiting adenosine triphosphate-citrate lyase (ACL) and consequently cholesterol biosynthesis, leading to increased expression of LDL receptors and increasing low-density lipoproteins (LDL-C) plasma clearence. It is a prodrug for oral administration with intracellular activation. It is activatedin liver cells and to a lesser extent in kidney cells, being absent in adipose tissue and muscle cells. Therefore, unlike statins, its potential myotoxic effect is very limited. It has recently been approved as a lipid-lowering drug in combination with diet, with statins, or with other lipid-lowering drugs in patients with hypercholesterolaemia, mixed dyslipidaemia, statin intolerance, or when these are contraindicated. The marketing of bempedoic acid implies, in clinical practice, having a new family of lipid-lowering drugs.

[21] *Mostaza JM, Lahoz C*. **Main barriers in the management of dyslipidaemias: Intolerants**. Clinica e investigacion en arteriosclerosis : publicacion oficial de la Sociedad Espanola de Arteriosclerosis 2021; 33 Suppl 1:40-45.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33966812
ABSTRACT

The lack of achieving the LDL-cholesterol goal observed in epidemiological studies, highlights the difficulty of transferring the benefit of the hypolipidaemic treatment noted in clinical trials, to current clinical practice. Although the reasons for not reaching LDL targets are probably multiple, i.e. treatment non-adherence, or therapeutic inertia, or treatment discontinuation as a consequence of statin intolerance, is frequently described. Statins are safe medications. However, 10 to 20% of the population refer to myalgias associated with their use, and 1 to 3% abandon treatment for this cause. In these subjects, it is necessary to change to a different statin, to use lower doses of statins, or to use irregular prescription regimes. If these actions are not useful, emphasis should be placed on the importance of hygienic and dietary recommendations and, when needed and depending on the cholesterol goal to achieve, the need of other lipid lowering treatments, like ezetimibe, bile acid sequestrants, bempedoic acid, or PCSK9i, often in combination.

[22] *Cohen H, Stefanutti C*. **Current Approach to the Diagnosis and Treatment of Heterozygote and Homozygous FH Children and Adolescents**. Current atherosclerosis reports 2021; 23:30.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33963467

ABSTRACT

PURPOSE OF REVIEW: To elucidate the current approach of care in pediatric patients with familial hypercholesterolemia (FH). We sought an answer to the question whether the advances and major changes in lipid management are relevant and apply to children and adolescents. RECENT FINDINGS: Latest research findings clearly demonstrate that lowering cholesterol levels at a young age prevents vascular atherosclerotic changes and decreases cardiovascular events in adulthood and emphasizes the importance of early detection and intervention in the pediatric FH patients group. FH is a common genetic disease caused by mutations in genes associated with the metabolism of low-density lipoproteins (LDL). The hallmark of FH is elevated LDL cholesterol (LDL-C) levels from birth and premature atherosclerotic cardiovascular disease (ASCVD). Often FH is either undiagnosed or diagnosed with a considerable delay, leading to vascular atherosclerotic changes and cardiovascular disease. Prompt identification of FH subjects is essential, to initiate early preventive measures. Safe and efficient pharmacological agents are approved for use in children and adolescents. Statins are the first line of therapy, in combination of ezetimibe. Unfortunately, these drugs do not warrant the achievement of therapeutic target, especially in HoFH patient. In the latter, lipoprotein apheresis (LA), which has been shown to be safe and effective, is strongly recommended. Finally, the new drugs still under study will allow a multimodal customized treatment. Lowering cholesterol levels at a young age hinders vascular atherosclerotic changes decreasing cardiovascular events in adulthood. Therefore, early detection, diagnosis, and intervention in FH patients are priority objectives.

[23] *Katsiki N, Pérez-Martínez P, Lopez-Miranda J*. **Olive Oil Intake and Cardiovascular Disease Prevention: "Seek and You Shall Find"**. Current cardiology reports 2021; 23:64.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33961163

ABSTRACT

PURPOSE OF REVIEW: The present narrative review focuses on the up-to-date clinical data on the correlations between olive oil consumption and cardiovascular (CV) diseases (i.e., CHD, stroke, and peripheral artery disease). RECENT FINDINGS: Olive oil contains monounsaturated fats, several antioxidant phenols, and other micronutrients that mediate CV-protective effects via improvements in

oxidative stress, endothelial dysfunction, inflammation, thrombosis, blood pressure, and lipid and carbohydrate metabolism. High consumption of olive oil, and in particular the extra-virgin, which is rich in phenolic antioxidants, has been suggested to prevent against coronary heart disease (CHD). The olive oil-induced cardioprotection was further supported by the findings of a very recent analysis of 2 large US prospective cohort studies showing that a higher olive oil intake was related to a lower risk of CV morbidity and mortality after 24 years of follow-up and that replacement of dairy fat, margarine, butter, or mayonnaise with the equivalent amount of olive oil significantly reduced CV risk. There is evidence for associations between olive oil consumption and lower risk for CV diseases. Both health policy makers and physicians should be aware of these associations and thus promote the intake of olive oil in both primary and secondary prevention settings to minimize individual's CV risk.

[24] *Soni M, Ambrosino M, Jacoby DS*. **The Use of Subclinical Atherosclerosis Imaging to Guide Preventive Cardiology Management**. Current cardiology reports 2021; 23:61.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33961134

ABSTRACT

PURPOSE OF THE REVIEW: Clinical atherosclerotic cardiovascular disease (ASCVD) requires years to manifest, providing a window of opportunity for preventive cardiovascular management. Subclinical atherosclerosis imaging leverages this long latency period to estimate and improve future ASCVD risk. RECENT FINDINGS: Coronary artery calcium (CAC) scoring has the most robust data in the detection of subclinical atherosclerosis. CAC scan significantly enhances cardiovascular risk stratification in addition to traditional risk models. Coronary computed tomography angiography data show similar strengths in subclinical atherosclerosis detection in addition to plaque morphology characterization with inherent limitations. Carotid intima-media thickness and ankle-brachial index are other modalities whose predictive value becomes incremental when added to the aforementioned modalities. When added to traditional risk models, subclinical atherosclerosis imaging modalities personalize future ASCVD risk stratification and assist in the initiation and rate of intensification of preventive therapies. Emerging imaging techniques exist but further research is required for primetime clinical use.

[25] *Britten-Jones AC, Kamel JT, Roberts LJ et al.* **Investigating the neuroPRotective effect of Oral Omega-3 Fatty acid Supplementation in type 1 diabetes (nPROOFS1): a randomised, placebo-controlled trial**. Diabetes 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33952620

ABSTRACT

This randomised, double-masked, placebo-controlled trial (ACTRN12618000705280) evaluated the effects of oral omega-3 fatty acid supplementation on peripheral nerves in type 1 diabetes. Participants with type 1 diabetes were assigned (1:1) to omega-3 (fish oil; 1800 mg/day) or placebo (olive oil; 600 mg/day) supplements for 180 days. Primary outcome was change from baseline in central corneal nerve fibre length (CNFL) at day 180. Secondary outcomes included change in other corneal nerve parameters, corneal sensitivity, peripheral small and large nerve fibre function, and ocular surface measures. Efficacy was analysed following intention-to-treat. Safety assessments included diabetic retinopathy grade and adverse events.Between July 2017 and September 2019, 43 participants received omega-3 (n=21) or placebo (n=22) supplements. All participants, except for two

assigned to placebo, completed the trial. At day 180, the estimated increase in CNFL in the omega-3 group, compared to placebo, was 2.70 mm/mm2 (95%CI: 1.64-3.75). The Omega-3 Index increased relative to placebo (3.3%; 95%CI: 2.4-4.2). There were no differences in most small or large nerve fibre functional parameters. Adverse events were similar between groups.In conclusion, this randomised controlled trial found that long-chain omega-3 supplements impart corneal neuroregenerative effects in type 1 diabetes, indicating a role in modulating peripheral nerve health.

[26] *Watanabe M, Balena A, Tuccinardi D et al.* **Central obesity, smoking habit, and hypertension are associated with lower antibody titres in response to COVID-19 mRNA vaccine**. Diabetes/metabolism research and reviews 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33955644
ABSTRACT
AIMS: To explore variables associated with the serological response following COVID-19 mRNA vaccine. METHODS: Eighty-six healthcare workers adhering to the vaccination campaign against COVID-19 were enrolled in January-February 2021. All subjects underwent two COVID-19 mRNA vaccine inoculations (Pfizer/BioNTech) separated by 3 weeks. Blood samples were collected before the 1st and 1-4 weeks after the second inoculation. Clinical history, demographics, and vaccine side effects were recorded. Baseline anthropometric parameters were measured, and body composition was performed through dual-energy-X-ray absorptiometry. RESULTS: Higher waist circumference was associated with lower antibody (Ab) titres (R = -0.324, p = 0.004); smokers had lower levels compared to non-smokers [1099 (1350) vs. 1921 (1375), p = 0.007], as well as hypertensive versus normotensive [650 ± 1192 vs. 1911 (1364), p = 0.001] and dyslipideamic compared to those with normal serum lipids [534 (972) vs 1872 (1406), p = 0.005]. Multivariate analysis showed that higher waist circumference, smoking, hypertension, and longer time elapsed since second vaccine inoculation were associated with lower Ab titres, independent of BMI, age. and gender. CONCLUSIONS: Central obesity, hypertension, and smoking are associated with lower Ab titres following COVID-19 vaccination. Although it is currently impossible to determine whether lower SARS-CoV-2 Abs lead to higher likelihood of developing COVID-19, it is well-established that neutralizing antibodies correlate with protection against several viruses including SARS-CoV-2. Our findings, therefore, call for a vigilant approach, as subjects with central obesity, hypertension, and smoking could benefit from earlier vaccine boosters or different vaccine schedules.

[27] *Bosch J, Lonn EM, Jung H et al.* **Lowering cholesterol, blood pressure, or both to prevent cardiovascular events: results of 8.7 years of follow-up of Heart Outcomes Evaluation Prevention (HOPE)-3 study participants**. European heart journal 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33963372
ABSTRACT
AIMS: Rosuvastatin (10 mg per day) compared with placebo reduced major adverse cardiovascular (CV) events by 24% in 12 705 participants at intermediate CV risk after 5.6 years. There was no benefit of blood pressure (BP) lowering treatment in the overall group, but a reduction in events in the third of participants with elevated systolic BP. After cessation of all the trial medications, we examined whether the benefits observed during the active treatment phase were sustained, enhanced, or attenuated. METHODS AND RESULTS: After the randomized treatment period (5.6 years), participants were invited to participate in 3.1 further years of observation (total 8.7 years). The first co-

primary outcome for the entire length of follow-up was the composite of myocardial infarction, stroke, or CV death [major adverse cardiovascular event (MACE)-1], and the second was MACE-1 plus resuscitated cardiac arrest, heart failure, or coronary revascularization (MACE-2). In total, 9326 (78%) of 11 994 surviving Heart Outcomes Prevention Evaluation (HOPE)-3 subjects consented to participate in extended follow-up. During 3.1 years of post-trial observation (total follow-up of 8.7 years), participants originally randomized to rosuvastatin compared with placebo had a 20% additional reduction in MACE-1 [95% confidence interval (CI), 0.64-0.99] and a 17% additional reduction in MACE-2 (95% CI 0.68-1.01). Therefore, over the 8.7 years of follow-up, there was a 21% reduction in MACE-1 (95% CI 0.69-0.90, P = 0.005) and 21% reduction in MACE-2 (95% CI 0.69-0.89, P = 0.002). There was no benefit of BP lowering in the overall study either during the active or post-trial observation period, however, a 24% reduction in MACE-1 was observed over 8.7 years. CONCLUSION: The CV benefits of rosuvastatin, and BP lowering in those with elevated systolic BP, compared with placebo continue to accrue for at least 3 years after cessation of randomized treatment in individuals without cardiovascular disease indicating a legacy effect. TRIAL REGISTRATION NUMBER: NCT00468923.

[28] *Kotseva K, De Backer G, De Bacquer D et al.* **Primary prevention efforts are poorly developed in people at high cardiovascular risk: A report from the European Society of Cardiology EURObservational Research Programme EUROASPIRE V survey in 16 European countries**. European journal of preventive cardiology 2021; 28:370-379.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33966079

ABSTRACT

BACKGROUND: European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE) V in primary care was carried out by the European Society of Cardiology EURObservational Research Programme in 2016-2018. The main objective was to determine whether the 2016 Joint European Societies' guidelines on cardiovascular disease prevention in people at high cardiovascular risk have been implemented in clinical practice. METHODS: The method used was a cross-stional survey in 78 centres from 16 European countries. Patients without a history of atherosclerotic cardiovascular disease either started on blood pressure and/or lipid and/or glucose lowering treatments were identified and interviewed ≥6 months after the start of medication. RESULTS: A total of 3562 medical records were reviewed and 2759 patients (57.6% women; mean age 59.0 ± 11.6 years) interviewed (interview rate 70.0%). The risk factor control was poor with 18.1% of patients being smokers, 43.5% obese (body mass index ≥30 kg/m2) and 63.8% centrally obese (waist circumference ≥88 cm for women, ≥102 cm for men). Of patients on blood pressure lowering medication 47.0% reached the target of <140/90 mm Hg (<140/85 mm Hg in people with diabetes). Among treated dyslipidaemic patients only 46.9% attained low density lipoprotein-cholesterol target of <2.6 mmol/l. Among people treated for type 2 diabetes mellitus, 65.2% achieved the HbA1c target of <7.0%. CONCLUSION: The primary care arm of the EUROASPIRE V survey revealed that large proportions of people at high cardiovascular disease risk have unhealthy lifestyles and inadequate control of blood pressure, lipids and diabetes. Thus, the potential to reduce the risk of future cardiovascular disease throughout Europe by improved preventive cardiology programmes is substantial.

[29] *do Brito Valente AF, Jaspers RT, Wüst RC*. **Regular physical exercise mediates the immune response in atherosclerosis**. Exerc Immunol Rev 2021; 27:42-53.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33965897
ABSTRACT
Atherosclerosis is a chronic inflammatory cardiovascular disease, which results from lipid accumulation in the blood vessel wall, forming a plaque, and ultimately restricting blood flow. The immune system plays a vital role in progression to plaque rupture. While recent evidence clearly indicates the anti-inflammatory function of regular exercise, the mechanisms by which regular exercise can modulate its pathophysiology is not well understood. In this review, we discuss how regular exercise can lower systemic inflammation directly via modulation of the immune system or indirectly via altered myokine concentrations and metabolites. We describe the exercise-induced responses of various myokines (such as IL-6, adiponectin, and FGF21), and how cell function in the innate immune system can be modulated via regular exercise, with the aim to modulate plaque formation in atherosclerosis.

[30] *Barrios V, Escobar C*. **Fixed-dose combination of rosuvastatin and ezetimibe: treating hypercholesteremia according to cardiovascular risk**. Expert Rev Clin Pharmacol 2021:1-14.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33970743
ABSTRACT
Introduction: Reducing low-density lipoprotein cholesterol (LDL-C) with lipid-lowering therapies has been associated with a decrease in the frequency of cardiovascular events.Areas covered: A systematic search was conducted on PubMed (MEDLINE), using the MeSH terms [Rosuvastatin] + [Ezetimibe] + [Dyslipidemia] + [treatment]. Original data from clinical trials, prospective and retrospective studies and more useful reviews were selected.Expert opinion: While statins continue to be the cornerstone of dyslipidemia management, many patients do not attain LDL-C targets with high-intensity statins alone. Rosuvastatin is a high-intensity statin with a low risk of adverse effects and drug-drug interactions and proven benefits in the prevention of cardiovascular disease. Rosuvastatin and ezetimibe have complementary mechanisms of action that enhance their ability to reduce LDL-C levels. Various studies have shown that the combination of rosuvastatin 10-40 mg and ezetimibe 10 mg enables considerable reductions in LDL-C (up to 60-75%) with a good safety profile in a broad spectrum of patients with hypercholesterolemia, including those at high risk and those with atherosclerotic cardiovascular disease. In addition, a fixed-dose combination of rosuvastatin and ezetimibe may improve adherence to medication. In this review, the available evidence on the combination of rosuvastatin and ezetimibe is updated.

[31] *Wu D, Yang Q, Su B et al.* **Low-Density Lipoprotein Cholesterol 4: The Notable Risk Factor of Coronary Artery Disease Development**. Frontiers in cardiovascular medicine 2021; 8:619386.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33937355
ABSTRACT
Background: Coronary artery disease (CAD) is the leading cause of death worldwide, which has a long asymptomatic period of atherosclerosis. Thus, it is crucial to develop efficient strategies or biomarkers to assess the risk of CAD in asymptomatic individuals. Methods: A total of 356 consecutive CAD patients and 164 non-CAD controls diagnosed using coronary angiography were recruited. Blood lipids, other baseline characteristics, and clinical information were investigated in this

study. In addition, low-density lipoprotein cholesterol (LDL-C) subfractions were classified and quantified using the Lipoprint system. Based on these data, we performed comprehensive analyses to investigate the risk factors for CAD development and to predict CAD risk. Results: Triglyceride, LDLC-3, LDLC-4, LDLC-5, LDLC-6, and total small and dense LDL-C were significantly higher in the CAD patients than those in the controls, whereas LDLC-1 and high-density lipoprotein cholesterol (HDL-C) had significantly lower levels in the CAD patients. Logistic regression analysis identified male [odds ratio (OR) = 2.875, $P < 0.001$], older age (OR = 1.018, $P = 0.025$), BMI (OR = 1.157, $P < 0.001$), smoking (OR = 4.554, $P < 0.001$), drinking (OR = 2.128, $P < 0.016$), hypertension (OR = 4.453, $P < 0.001$), and diabetes mellitus (OR = 8.776, $P < 0.001$) as clinical risk factors for CAD development. Among blood lipids, LDLC-3 (OR = 1.565, $P < 0.001$), LDLC-4 (OR = 3.566, $P < 0.001$), and LDLC-5 (OR = 6.866, $P < 0.001$) were identified as risk factors. To predict CAD risk, six machine learning models were constructed. The XGboost model showed the highest AUC score (0.945121), which could distinguish CAD patients from the controls with a high accuracy. LDLC-4 played the most important role in model construction. Conclusions: The established models showed good performance for CAD risk prediction, which can help screen high-risk CAD patients in asymptomatic population, so that further examination and prevention treatment might be taken before any sudden or serious event.

[32] *Collado A, Domingo E, Marques P et al.* **Oral Unsaturated Fat Load Impairs Postprandial Systemic Inflammation in Primary Hypercholesterolemia Patients**. Frontiers in pharmacology 2021; 12:656244.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33959024

ABSTRACT

Context: Primary hypercholesterolemia (PH) is a lipid disorder characterized by elevated levels of cholesterol and low-density lipoprotein (LDL). Low-grade systemic inflammation is associated with PH, which might explain the higher incidence of cardiovascular diseases in this setting. Objective: To evaluate the effect of an oral unsaturated fat load (OUFL) on different immune parameters and functional consequences in patients with PH in postprandial state. Design: A commercial liquid preparation of long-chain triglycerides (Supracal(®); ω6/ω3 ratio >20/1, OUFL) was administered to 20 patients and 10 age-matched controls. Whole blood was collected before (fasting state) and 4 h after administration (postprandial state). Flow cytometry was employed to determine platelet and leukocyte activation, and the levels of circulating platelet-leukocyte aggregates. Soluble markers were determined by ELISA, and the parallel-plate flow chamber was employed to study leukocyte adhesion to the dysfunctional arterial endothelium. Results: The PH group had a lower percentage of activated platelets and circulating type 1 monocytes, and blunted neutrophil activation after the OUFL, accompanied by a significant increase in the percentage of regulatory T lymphocytes. In this group, the OUFL led to a significant impairment of leukocyte adhesion to the dysfunctional [tumor necrosis factor α (TNFα)-stimulated] endothelium and reduced the plasma levels of soluble P-selectin, platelet factor-4 (PF-4)/CXCL4, CXCL8, CCL2, CCL5, and TNFα. Conclusion: The OUFL has a beneficial impact on the pro-thrombotic and pro-inflammatory state of PH patients and might be a promising macronutrient approach to dampen the systemic inflammation associated with PH and the development of further cardiovascular events.

[33] *Liang Z, Chen Q, Wei R et al.* **Cost-Effectiveness of Alirocumab for the Secondary Prevention of Cardiovascular Events after Myocardial Infarction in the Chinese Setting**. Frontiers in pharmacology 2021; 12:648244.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33935749

ABSTRACT

Background: Proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab reduce ischemic events; however, the cost-effectiveness remains uncertain. This study sought to evaluate its economic value in patients with myocardial infarction (MI) from the Chinese healthcare perspective. Methods: A state-transition Markov model was developed to determine the cost-effectiveness of alirocumab for preventing recurrent MI, ischemic stroke and death. Preventative effect of the therapy was gathered from ODYSSEY OUTCOMES trial and absolute reduction of low-density lipoprotein cholesterol (LDL-C) in ODYSSEY EAST trial, respectively. The primary outcome was the incremental cost-effectiveness ratio (ICER), defined as incremental cost per quality-adjusted life-year (QALY) gained. Results: Compared with statin monotherapy, the ICER of alirocumab therapy at its present discounted price [34,355 Chinese yuan (CNY) annually, 33% rebate] based on clinical follow-up efficacy was 1,613,997 CNY per QALY gained. A willingness-to-pay threshold of 212,676 CNY per QALY would be achieved when the annual cost of alirocumab was reduced by 88% from the full official price to 6071 CNY. The therapeutic effect evaluation estimated by the magnitude of LDL-C reduction was superior to the results of clinical follow-up, but this medication was still far from cost-effective. Multiple vulnerable subgroup analyses demonstrated that the ICER for patients with polyvascular disease in 3 vascular beds was 111,750 CNY per QALY gained. Conclusion: Alirocumab is not cost-effective in general MI population based on current discounted price. High long-term costs of alirocumab may be offset by health benefit in patients with polyvascular disease (3 beds).

[34] *Torti C, Scaglione V, Cesana BM et al.* **Effect of directly acting antivirals for hepatitis C virus infection on proprotein convertase subtilisin/kexin type 9 level**. Health science reports 2021; 4:e273.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33969232

ABSTRACT

BACKGROUND AND AIMS: Eradication of the hepatitis C virus (HCV) may affect proprotein convertase subtilisin/kexin type 9 (PCSK9) levels and cardiovascular risk. However, information regarding PCSK9 level after HCV eradication is lacking. Hence, in this case-control retrospective study, we aimed to evaluate PCSK9 level from pretherapy baseline up to sustained virological response (SVR). METHODS: Eighty-four patients treated with directly acting antivirals (DAAs) between July 2015 and May 2018 were enrolled. Differences in baseline PCSK9 level due to absence/presence of recorded baseline characteristics (covariates) were evaluated. Changes in PCSK9 levels from pretherapy to SVR (ΔPCSK9) and their correlations with the covariates were assessed. The repeated measures analysis of variance was used to investigate the differences in PCSK9 level from the baseline to the achievement of SVR due to absence/presence of any covariate. RESULTS: The mean age of the patients was 67.6 ± 11 years, and 53.6% were males. Baseline PCSK9 levels were statistically lower in patients using statins than in those not using statins (mean, 70.3 ± 43.1 ng/mL vs 271.8 ± 252.2 ng/mL; P = .017). PCSK9 level decreased significantly from baseline to the time of SVR (255 ± 248 ng/mL vs 169 ± 188 ng/mL; P < .001). PCSK9 levels were statistically higher in the HCV-infected patients at baseline than in the control group (255 ± 248 vs

166.3 ± 120.2 ng/mL; P = .020); however, this difference was lost after achieving SVR (mean, 169 ± 188 vs 166.3 ± 120.2 ng/mL; P = .464). Changes in PCSK9 level was not statistically related to any of the recorded covariates. The PCSK9 mean level did not differ significantly with absence/presence of any covariate from pretherapy to SVR. CONCLUSIONS: The reduction in mean PCSK9 level from baseline pretherapy to after HCV eradication was statistically significant. Whether PCSK9 is a new biomarker for cardiovascular risk in these patients remains to be ascertained.

[35] *Poznyak AV, Bezsonov EE, Eid AH et al.* **ACE2 Is an Adjacent Element of Atherosclerosis and COVID-19 Pathogenesis**. International journal of molecular sciences 2021; 22.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33946649

ABSTRACT

COVID-19 is a highly contagious new infection caused by the single-stranded RNA Sars-CoV-2 virus. For the first time, this infection was recorded in December 2019 in the Chinese province of Wuhan. The virus presumably crossed the interspecies barrier and passed to humans from a bat. Initially, the disease was considered exclusively in the context of damage to the respiratory system, but it quickly became clear that the disease also entails serious consequences from various systems, including the cardiovascular system. Among these consequences are myocarditis, myocardial damage, subsequent heart failure, myocardial infarction, and Takotsubo syndrome. On the other hand, clinical data indicate that the presence of chronic diseases in a patient aggravates the course and outcome of coronavirus infection. In this context, the relationship between COVID-19 and atherosclerosis, a condition preceding cardiovascular disease and other disorders of the heart and blood vessels, is particularly interesting. The renin-angiotensin system is essential for the pathogenesis of both coronavirus disease and atherosclerosis. In particular, it has been shown that ACE2, an angiotensin-converting enzyme 2, plays a key role in Sars-CoV-2 infection due to its receptor activity. It is noteworthy that this enzyme is important for the normal functioning of the cardiovascular system. Disruptions in its production and functioning can lead to various disorders, including atherosclerosis.

[36] *Miao J, Bachmann KN, Huang S et al.* **Effects of Vitamin D Supplementation on Cardiovascular and Glycemic Biomarkers**. Journal of the American Heart Association 2021; 10:e017727.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33960201

ABSTRACT

Background Experimental and observational studies have suggested a link between vitamin D and cardiovascular and metabolic disease, but this has not been confirmed in randomized controlled trials. We sought to determine whether vitamin D supplementation reduces biomarkers of insulin resistance, inflammation, neurohormonal activation, and lipids. Methods and Results This was a prespecified, secondary analysis of the DAYLIGHT (Vitamin D Therapy in Individuals at High Risk of Hypertension) randomized controlled trial. We measured circulating homeostatic model assessment of insulin resistance, hs-CRP (high-sensitivity C-reactive protein), N-terminal pro-B-type natriuretic peptide, renin, aldosterone, and lipids at baseline and at 6 months in 289 individuals with low vitamin D status (25-hydroxyvitamin-D [25-OH-D] ≤25 ng/mL) receiving low-dose (400 IU/d) versus high-dose (4000 IU/d) vitamin D3 for 6 months. A meta-analysis of randomized controlled trials reporting biomarker changes after vitamin D supplementation was then performed. Levels of 25-OH-D increased in the high-dose relative to the low-dose vitamin D group (+15.5 versus +4.6 ng/mL,

P<0.001). Changes in biomarkers of glycemia, inflammation, and neurohormonal activation did not differ by dose. Lipids did not differ between groups, other than triglycerides, which increased in the high-dose compared with the low-dose group (+11.3 versus -6.2 mg/dL, P<0.001). The meta-analysis showed potential modest decreases in homeostatic model assessment of insulin resistance and hs-CRP, but no changes in low-density lipoprotein, after vitamin D supplementation compared with control groups. Conclusions In the DAYLIGHT randomized controlled trial, high-dose vitamin D supplementation did not improve biomarkers of glycemia, inflammation, neurohormonal activation, or lipids. Registration URL: https://www.clinicaltrials.gov; Unique identifier: NCT01240512.

[37] *Duggal V, Thomas IC, Montez-Rath ME et al.* **National Estimates of CKD Prevalence and Potential Impact of Estimating Glomerular Filtration Rate Without Race**. Journal of the American Society of Nephrology : JASN 2021; 32:1454-1463.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33958490

ABSTRACT

BACKGROUND: The implications of removing the adjustment for Black race in equations to eGFR on the prevalence of CKD and management strategies are incompletely understood. METHODS: We estimated changes in CKD prevalence and the potential effect on therapeutic drug prescriptions and prediction of kidney failure if race adjustment were removed from the CKD-EPI GFR estimating equation. We used cross-sectional and longitudinal data from adults aged ≥18 years in the National Health and Nutrition Examination Survey (NHANES) from 2015 to 2016, and the Veterans Affairs (VA) Health Care System in 2015. In the VA cohort, we assessed use of common medications that require dose adjustment on the basis of kidney function, and compared the prognostic accuracy of the Kidney Failure Risk Equation with versus without race adjustment of eGFR. RESULTS: The prevalence of CKD among Black adults increased from 5.2% to 10.6% in NHANES, and from 12.4% to 21.6% in the VA cohort after eliminating race adjustment. Among Black veterans, 41.0% of gabapentin users, 33.5% of ciprofloxacin users, 24.0% of metformin users, 6.9% of atenolol users, 6.6% of rosuvastatin users, and 5.8% of tramadol users were reclassified to a lower eGFR for which dose adjustment or discontinuation is recommended. Without race adjustment of eGFR, discrimination of the Kidney Failure Risk Equation among Black adults remained high and calibration was marginally improved overall, with better calibration at higher levels of predicted risk. CONCLUSIONS: Removal of race adjustment from CKD-EPI eGFR would double the estimated prevalence of CKD among Black adults in the United States. Such a change is likely to affect a sizeable number of drug-dosing decisions. It may also improve the accuracy of kidney failure risk prediction among higher-risk Black adults.

[38] *Hirano T, Kodera R, Hirashima T et al.* **Metabolic Properties of Lowdensity Lipoprotein (LDL) Triglycerides in Patients with Type 2 Diabetes, Comparison with Small Dense LDL-Cholesterol**. Journal of atherosclerosis and thrombosis 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33952832

ABSTRACT

AIMS: Abnormal compositional changes in low-density lipoprotein (LDL) particles, such as triglyceride (TG) enrichment and size reduction, are common in patients with diabetes. Several cohort studies have demonstrated that LDL-TG and sdLDL-cholesterol (C) are sensitive biomarkers for predicting atherosclerotic cardiovascular diseases beyond LDL-C. Although sdLDL has been extensively

studied, little is known about the properties of LDL-TG. We investigated similarities or differences between LDL-TG and sdLDL-C. METHODS: Fasting plasma was obtained from 1,085 patients with type 2 diabetes who were enrolled in the diabetes regional cohort study (ViNA Cohort). LDL-TG and sdLDL-C concentrations were measured using a homogeneous assay established by us. In a subset of subjects, LDL-TG and sdLDL-C levels were measured postprandially or after treatment with lipid-lowering drugs. RESULTS: In a quartile analysis, higher LDL-TG quartiles were associated with higher frequency of female and fibrate users, whereas sdLDL-C quartiles were associated with frequency of men, drinking, and metabolic syndrome-related measurements. Higher quartiles of LDL-TG/LDL-C were associated with smoking, drinking, fibrate users, and statin users. LDL-TG was significantly correlated with TG, LDL-C, sdLDL-C, and apolipoprotein (apo) B, with apoB being the primary determinant. LDL-TG correlated to high sensitive C-reactive protein (CRP) independently of other lipids. Mean LDL-TG did not change with fasting/non-fasting. Statin treatment reduced LDL-TG, whereas fibrates increased it, but these drugs reduced sdLDL-C equally. CONCLUSIONS: LDL-TG levels were more tightly regulated by the number of LDL particles than plasma TG levels were. SdLDL-C was closely associated with metabolic syndrome-related factors, whereas LDL-TG was associated with low-grade systemic inflammation.

[39] *Komatsu T, Ayaori M, Uto-Kondo H et al.* **Atorvastatin Reduces Circulating S100A12 Levels in Patients with Carotid Atherosclerotic Plaques - A Link with Plaque Inflammation**. Journal of atherosclerosis and thrombosis 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33952812
ABSTRACT
AIMS: Inflammation is involved in various processes of atherosclerosis development. Serum C-reactive protein (CRP) levels, a predictor for cardiovascular risk, are reportedly reduced by statins. However, several studies have demonstrated that CRP is a bystander during atherogenesis. While S100A12 has been focused on as an inflammatory molecule, it remains unclear whether statins affect circulating S100A12 levels. Here, we investigated whether atorvastatin treatment affected S100A12 and which biomarkers were correlated with changes in arterial inflammation. METHODS: We performed a prospective, randomized open-labeled trial on whether atorvastatin affected arterial (carotid and thoracic aorta) inflammation using (18)fluorodeoxyglucose positron emission tomography/computed tomography ((18)F-FDG-PET/CT) and inflammatory markers. Thirty-one statin-naïve patients with carotid atherosclerotic plaques were randomized to either a group receiving dietary management (n=15) or one receiving atorvastatin (10mg/day, n=16) for 12weeks. (18)F-FDG-PET/CT and flow-mediated vasodilation (FMD) were performed, the latter to evaluate endothelial function. RESULTS: Atorvastatin, but not the diet-only treatment, significantly reduced LDL-cholesterol (LDL-C, -43%), serum CRP (-37%) and S100A12 levels (-28%) and improved FMD (+38%). (18)F-FDG-PET/CT demonstrated that atorvastatin, but not the diet-only treatment, significantly reduced accumulation of (18)F-FDG in the carotid artery and thoracic aorta. A multivariate analysis revealed that reduction in CRP, S100A12, LDL-C, oxidized-LDL, and increase in FMD were significantly associated with reduced arterial inflammation in the thoracic aorta, but not in the carotid artery. CONCLUSIONS: Atorvastatin treatment reduced S100A12/CRP levels, and the changes in these circulating markers mirrored the improvement in arterial inflammation. Our observations suggest that S100A12 may be an emerging therapeutic target for atherosclerosis.

[40] *Ramos-Rincón JM, Pérez-Belmonte LM, Carrasco-Sánchez FJ et al.* **Cardiometabolic therapy and mortality in very old patients with diabetes hospitalized due to COVID-19**. J Gerontol A Biol Sci Med Sci 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33945610
ABSTRACT
BACKGROUND: The effects of cardiometabolic drugs on the prognosis of diabetic patients with COVID-19, especially very old patients, are not well-known. This work aims to analyze the association between preadmission cardiometabolic therapy (antidiabetic, antiaggregant, antihypertensive, and lipid-lowering drugs) and in-hospital mortality among patients ≥80 years with type 2 diabetes mellitus hospitalized for COVID-19. METHODS: We conducted a nationwide, multicenter, observational study in patients ≥80 years with type 2 diabetes mellitus hospitalized for COVID-19 between March 1 and May 29, 2020. The primary outcome measure was in-hospital mortality. A multivariate logistic regression analysis were performed to assess the association between preadmission cardiometabolic therapy and in-hospital mortality. RESULTS: Of the 2,763 patients ≥80 years old hospitalized due to COVID-19, 790 (28.6%) had T2DM. Of these patients, 385 (48.7%) died during admission. On the multivariate analysis, the use of dipeptidyl peptidase-4 inhibitors (AOR 0.502, 95%CI 0.309-0.815, p=0.005) and angiotensin receptor blockers (AOR 0.454, 95%CI 0.274-0.759, p=0.003) were independent protectors against in-hospital mortality whereas the use of acetylsalicylic acid was associated with higher in-hospital mortality (AOR 1.761, 95%CI 1.092-2.842, p=0.020). Other antidiabetic drugs, angiotensin-converting enzyme inhibitors and statins showed neutral association with in-hospital mortality. CONCLUSIONS: We found important differences between cardiometabolic drugs and in-hospital mortality in older patients with type 2 diabetes mellitus hospitalized for COVID-19. Preadmission treatment with dipeptidyl peptidase-4 inhibitors and angiotensin receptor blockers could reduce in-hospital mortality; other antidiabetic drugs, angiotensin-converting enzyme inhibitors and statins seem to have a neutral effect; and acetylsalicylic acid could be associated with excess mortality.

[41] *Benedek P, Jiao H, Duvefelt K et al.* **Founder effects facilitate the use of a genotyping-based approach to molecular diagnosis in Swedish patients with familial hypercholesterolaemia**. Journal of internal medicine 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33955087
ABSTRACT
AIM: To investigate whether genotyping could be used as a cost-effective screening step, preceding next-generation sequencing (NGS), in molecular diagnosis of familial hypercholesterolaemia (FH) in Swedish patients. METHODS AND RESULTS: Three hundred patients of Swedish origin with clinical suspicion of heterozygous FH were analysed using a specific array genotyping panel embedding 112 FH-causing mutations in the LDLR, APOB and PCSK9 genes. The mutations had been selected from previous reports on FH patients in Scandinavia and Finland. Mutation-negative cases were further analysed by NGS. In 181 patients with probable or definite FH using the Dutch lipid clinics network (DLCN) criteria (score ≥ 6), a causative mutation was identified in 116 (64%). Of these, 94 (81%) were detected by genotyping. Ten mutations accounted for more than 50% of the positive cases, with APOB c.10580G>A being the most common. Mutations in LDLR predominated, with (c.2311+1_2312-1)(2514)del (FH Helsinki) and c.259T>G having the highest frequency. Two novel LDLR mutations were identified. In patients with DLCN score < 6, mutation detection rate was significantly higher at

younger age. CONCLUSION: A limited number of mutations explain a major fraction of FH cases in Sweden. Combination of selective genotyping and NGS facilitates the clinical challenge of cost-effective genetic screening in suspected FH. The frequency of APOB c.10580G>A was higher than previously reported in Sweden. The lack of demonstrable mutations in the LDLR, APOB and PCSK9 genes in ~1/3 of patients with probable FH strongly suggests that additional genetic mechanisms are to be found in phenotypic FH.

[42] *Saha A, Garg A*. **Severe Liver Injury Associated With High-Dose Atorvastatin Therapy**. Journal of investigative medicine high impact case reports 2021; 9:23247096211014050.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33966478

ABSTRACT

Statins are recommended for first-line management of elevated cholesterol in the primary and secondary prevention of atherosclerotic cardiovascular disease. Statins may occasionally be associated with mild transaminase elevations but can also result in life-threatening liver injury. Atorvastatin is the most common cause of clinically significant liver injury in this drug class. We report a case of severe, asymptomatic liver injury in a hepatocellular pattern in a 71-year-old man occurring within 3 months of switching from simvastatin to high-intensity atorvastatin therapy. Hepatitis improved rapidly with cessation of atorvastatin and did not recur after resuming simvastatin.

[43] *Tian LQ, Yu YT, Jin MD et al.* **Early 1,25-Dihydroxyvitamin D(3) Supplementation Effectively Lowers the Incidence of Type 2 Diabetes Mellitus via Ameliorating Inflammation In KK-A(y) Mice**. Journal of nutritional science and vitaminology 2021; 67:84-90.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33952739

ABSTRACT

Few studies have been performed to investigate the effect of vitamin D supplementation and T2DM in type 2 diabetic animal models. The present study aimed to explore the relationship between early 1,25-dihydroxyvitamin D(3) [1,25(OH)(2)D(3)] and the incidence of T2DM and determine whether early 1,25(OH)(2)D(3) supplementation was associated with inflammation in KK-A(y) mice. The KK-A(y) mice were divided into 4 vitamin D treatment groups, the low-dose vitamin D supplementation group (VDS-L, 1.5 μg/kg 1,25(OH)(2)D(3)), moderate-dose vitamin D supplementation group (VDS-M, 3.0 μg/kg 1,25(OH)(2)D(3)), high-dose vitamin D supplementation group (VDS-H, 6.0 μg/kg 1,25(OH)(2)D(3)) and the model control group (MC). C57BL/6J mice were used as the controls. The treatment period lasted for 9 wk. During this treatment period, fasting blood glucose (FBG) level of the mice was measured on a weekly basis. The levels of lipid profile, insulin and inflammation biomarkers were determined after 9 wk of 1,25(OH)(2)D(3) intragastric gavage. After 9 wk of 1,25(OH)(2)D(3) intragastric gavage, FBG level was significantly decreased in the vitamin D treatment groups compared with the MC group. The number of T2DM incidence in the VDS-L group (n=7), VDS-M group (n=5) and VDS-H group (n=3) was lower than those in the MC group (n=10) on week 9. Moreover, serum C-reactive protein (CRP) and interleukin-6 (IL-6) in the vitamin D treatment groups were significantly suppressed by 1,25(OH)(2)D(3) administration compared with the MC group. Early 1,25(OH)(2)D(3) supplementation could effectively lower the incidence of T2DM via ameliorating inflammation in KK-A(y) mice.

[44] *Ward ED, Thomasson K, Fischer KR*. **Analysis of Omega-3 Fatty Acid Content in Fish Oil Products**. Journal of pharmacy practice 2021:8830738211015051.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33955300

ABSTRACT

BACKGROUND: Omega-3 fatty acids eicosapentaenoic acid (EPA) and docosehexaenoic acid (DHA), often found in fish oil supplements, have been linked to cardiovascular benefits in proper doses. OBJECTIVES: Quantify serving sizes and EPA and DHA content of fish oil products and determine which products contain appropriate amounts of EPA and DHA per serving to lower cholesterol. METHODS: Products were identified through the National Institutes of Health's Dietary Supplement Label Database using the search term "fish oil." Product labels were reviewed for EPA and DHA content. The number of units, such as capsules, gummies, or milliliters, necessary to obtain a total of at least 2,000 mg of EPA and DHA was also evaluated. Descriptive statistics were used to report findings. RESULTS: Of 493 products identified, 231 products were analyzed. Two (0.9%) products, both of which were liquid formulations, contained at least 2,000 mg of EPA and DHA in the standard serving size listed on the labeling. The total amount of EPA and DHA per serving ranged from 60.2 mg to 2684 mg with an average of 697 mg. The number of servings necessary to achieve 2,000 mg of EPA and DHA ranged from 1 to 34 servings with an average of 5 servings. CONCLUSIONS: Serving sizes of fish oil products rarely result in adequate EPA and DHA intake to provide cholesterol-lowering benefit. Instruction by a trained healthcare professional, such as a pharmacist, is important to ensure patients are taking an appropriate serving of fish oil to obtain cardiovascular benefit.

[45] *Joshi PH, de Lemos JA*. **Diagnosis and Management of Stable Angina: A Review**. Jama 2021; 325:1765-1778.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33944871

ABSTRACT

IMPORTANCE: Nearly 10 million US adults experience stable angina, which occurs when myocardial oxygen supply does not meet demand, resulting in myocardial ischemia. Stable angina is associated with an average annual risk of 3% to 4% for myocardial infarction or death. Diagnostic tests and medical therapies for stable angina have evolved over the last decade with a better understanding of the optimal use of coronary revascularization. OBSERVATIONS: Coronary computed tomographic angiography is a first-line diagnostic test in the evaluation of patients with stable angina due to higher sensitivity and comparable specificity compared with imaging-based stress testing. Moreover, coronary computed tomographic angiography allows detection of nonobstructive atherosclerosis that would not be identified with other noninvasive imaging modalities, improving risk assessment and potentially triggering more appropriate allocation of preventive therapies. Novel therapies treating lipids (proprotein convertase subtilisin/kexin type 9 inhibitors, ezetimibe, and icosapent ethyl) and type 2 diabetes (sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide 1 receptor agonists) have improved cardiovascular outcomes in patients with stable ischemic heart disease when added to usual care. Randomized clinical trials showed no improvement in the rates of mortality or myocardial infarction with revascularization (largely by percutaneous coronary intervention) compared with optimal medical therapy alone, even in the setting of moderate to severe ischemia. In contrast, revascularization provides a meaningful benefit on angina and quality of life compared with antianginal therapies. Measures of the effect of angina on a patient's quality of life should be

integrated into the clinic encounter to assist with the decision to proceed with revascularization. CONCLUSIONS AND RELEVANCE: For patients with stable angina, emphasis should be placed on optimizing lifestyle factors and preventive medications such as lipid-lowering and antiplatelet agents to reduce the risk for cardiovascular events and death. Antianginal medications, such as β-blockers, nitrates, or calcium channel blockers, should be initiated to improve angina symptoms. Revascularization with percutaneous coronary intervention should be reserved for patients in whom angina symptoms negatively influence quality of life, generally after a trial of antianginal medical therapy. Shared decision-making with an informed patient is important for effective treatment of stable angina.

[46] *Barankay I, Reese PP, Putt ME et al.* **Qualitative Exploration of Barriers to Statin Adherence and Lipid Control: A Secondary Analysis of a Randomized Clinical Trial**. JAMA network open 2021; 4:e219211.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33944923

ABSTRACT
IMPORTANCE: Financial incentives may improve health by rewarding patients for focusing on present actions-such as medication regimen adherence-that provide longer-term health benefits. OBJECTIVE: To identify barriers to improving statin therapy adherence and control of cholesterol levels with financial incentives and insights for the design of future interventions. DESIGN, SETTING, AND PARTICIPANTS: This qualitative study involved retrospective interviews with participants in a preplanned secondary analysis of a randomized clinical trial of financial incentives for statin therapy adherence. A total of 636 trial participants from several US insurer or employer populations and an academic health system were rank ordered by change in low-density lipoprotein cholesterol (LDLC) levels. Participants with the most LDLC level improvement (high-improvement group) and those with LDLC levels that did not improve (nonimprovement group) were purposively targeted, stratified across all trial groups, for semistructured telephone interviews that were performed from April 1 to June 30, 2018. Interviews were coded using a team-based, iterative approach. Data were analyzed from July 1, 2018, to October 31, 2020. MAIN OUTCOMES AND MEASURES: The primary outcome was mean change in LDLC level from baseline to 12 months; the secondary outcome, statin therapy adherence during the first 6 months. RESULTS: A total of 54 patients were interviewed, divided equally between high-improvement and nonimprovement groups, with a mean (SD) age of 43.5 (10.3) years; 36 (66.7%) were women, 28 (51.9%) had diabetes, and 18 (33.3%) had cardiovascular disease. Compared with the high-improvement group, the nonimprovement group had fewer interviewees with an annual income of greater than $50 000 (11 [40.7%] vs 22 [81.5%]), worse self-reported health (fair to poor, 13 [48.1%] vs 3 [11.1%]), more Black interviewees (16 [59.3%] vs 4 [14.8%]), and lower baseline LDLC levels (>160 mg/dL, 2 [7.4%] vs 25 [92.6%]). Participants in the nonimprovement group had a greater burden of chronic illness (≥2 chronic conditions, 13 [48.1%] vs 6 [22.2%]) and were less frequently employed (full-time, 6 [22.2%] vs 12 [44.4%]). In interviews, the nonimprovement group was less focused on risks of high LDLC levels, described less engagement in LDLC level management, articulated fewer specific nutritional choices for optimizing health, and recounted greater difficulty obtaining healthy food. Participants in both groups had difficulty describing the structure of the financial incentives but did recall features of the electronic pill containers used to track adherence and how those containers affected medication routines. CONCLUSIONS AND RELEVANCE: Participants in a statin adherence trial whose LDLC levels did not improve found it

more difficult to create medication routines and respond to financial incentives in the context of complex living conditions and a high burden of chronic illness. These findings suggest that future studies should be more attentive to socioeconomic circumstances of trial participants. TRIAL REGISTRATION: ClinicalTrials.gov Identifier: NCT01798784.

[47] *Yao H, Farnier M, Tribouillard L et al.* **Coronary lesion complexity in patients with heterozygous familial hypercholesterolemia hospitalized for acute myocardial infarction: data from the RICO survey**. Lipids in health and disease 2021; 20:45.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33947397
ABSTRACT
BACKGROUND: Although patients with familial heterozygous hypercholesterolemia (FH) have a high risk of early myocardial infarction (MI), the coronary artery disease (CAD) burden in FH patients with acute MI remains to be investigated. METHODS: The data for all consecutive patients hospitalized in 2012-2019 for an acute MI and who underwent coronary angiography were collected from a multicenter database (RICO database). FH (n = 120) was diagnosed using Dutch Lipid Clinic Network criteria (score ≥ 6). We compared the angiographic features of MI patients with and without FH (score 0-2) (n = 234) after matching for age, sex, and diabetes (1:2). RESULTS: Although LDL-cholesterol was high (208 [174-239] mg/dl), less than half of FH patients had chronic statin treatment. When compared with non-FH patients, FH increased the extent of CAD (as assessed by SYNTAX score; P = 0.005), and was associated with more frequent multivessel disease (P = 0.004), multiple complex lesions (P = 0.022) and significant stenosis location on left circumflex and right coronary arteries. Moreover, FH patients had more multiple lesions, with an increased rate of bifurcation lesions or calcifications (P = 0.021 and P = 0.036, respectively). In multivariate analysis, LDL-cholesterol levels (OR 1.948; 95% CI 1.090-3.480, P = 0.024) remained an independent estimator of anatomical complexity of coronary lesions, in addition to age (OR 1.035; 95% CI 1.014-1.057, P = 0.001). CONCLUSIONS: FH patients with acute MI had more severe CAD, characterized by complex anatomical features that are mainly dependent on the LDL-cholesterol burden. Our findings reinforce the need for more aggressive preventive strategies in these high-risk patients, and for intensive lipid-lowering therapy as secondary prevention.

[48] *Tseng AS, Girardo M, Firth C et al.* **Lower Extremity Arterial Disease as a Predictor of Incident Atrial Fibrillation and Cardiovascular Events**. Mayo Clinic proceedings 2021; 96:1175-1183.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33958054
ABSTRACT
OBJECTIVE: To evaluate the relationship between peripheral arterial disease (PAD) and incident atrial fibrillation (AF) and its clinical and pathophysiologic implications on ischemic stroke and all-cause mortality. PATIENTS AND METHODS: We identified all adult patients in the Mayo Clinic Health System without a previous diagnosis of AF undergoing ankle-brachial index (ABI) testing for any indication from January 1, 1996, to June 30, 2018. Retrospective extraction of ABI data and baseline echocardiographic data was performed. The primary outcome of interest was incident AF. The secondary outcomes of interest were incident ischemic stroke and all-cause mortality. RESULTS: A total of 33,734 patients were included in the study. After adjusting for demographic and comorbidity variables, compared with patients who had normal ABI (1.0 to 1.39), there was an increased risk of

incident AF in patients with low ABI (<1.0) (adjusted hazard ratio, 1.14; 95% CI, 1.06 to 1.22) and elevated ABI (≥1.4) (adjusted hazard ratio, 1.18; 95% CI, 1.06 to 1.31). The risk was greater in patients with increasing severity of PAD. Patients with abnormal ABIs had an increased risk of ischemic stroke and all-cause mortality. We found that patients with PAD and incident AF have certain baseline echocardiographic abnormalities. CONCLUSION: In this large cohort of ambulatory patients undergoing ABI measurement, patients with PAD were at increased risk for incident AF, ischemic stroke, and mortality. In these high-risk patients with abnormal ABI, particularly severe PAD and cardiac structural abnormalities, routine monitoring for AF and management of cardiovascular risk factors may be warranted.

[49] *Jennings GL, Audehm R, Bishop W et al.* **National Heart Foundation of Australia: position statement on coronary artery calcium scoring for the primary prevention of cardiovascular disease in Australia**. The Medical journal of Australia 2021; 214:434-439.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33960402

ABSTRACT

This position statement considers the evolving evidence on the use of coronary artery calcium scoring (CAC) for defining cardiovascular risk in the context of Australian practice and provides advice to health professionals regarding the use of CAC scoring in primary prevention of cardiovascular disease in Australia. Main recommendations: CAC scoring could be considered for selected people with moderate absolute cardiovascular risk, as assessed by the National Vascular Disease Prevention Alliance (NVDPA) absolute cardiovascular risk algorithm, and for whom the findings are likely to influence the intensity of risk management. (GRADE evidence certainty: Low. GRADE recommendation strength: Conditional.) CAC scoring could be considered for selected people with low absolute cardiovascular risk, as assessed by the NVDPA absolute cardiovascular risk algorithm, and who have additional risk-enhancing factors that may result in the underestimation of risk. (GRADE evidence certainty: Low. GRADE recommendation strength: Conditional.) If CAC scoring is undertaken, a CAC score of 0 AU could reclassify a person to a low absolute cardiovascular risk status, with subsequent management to be informed by patient-clinician discussion and follow contemporary recommendations for low absolute cardiovascular risk. (GRADE evidence certainty: Very low. GRADE recommendation strength: Conditional.) If CAC scoring is undertaken, a CAC score > 99 AU or ≥ 75th percentile for age and sex could reclassify a person to a high absolute cardiovascular risk status, with subsequent management to be informed by patient-clinician discussion and follow contemporary recommendations for high absolute cardiovascular risk. (GRADE evidence certainty: Very low. GRADE recommendation strength: Conditional.) CHANGES IN MANAGEMENT AS A RESULT OF THIS STATEMENT: CAC scoring can have a role in reclassification of absolute cardiovascular risk for selected patients in Australia, in conjunction with traditional absolute risk assessment and as part of a shared decision-making approach that considers the preferences and values of individual patients.

[50] *Matta A, Bongard V, Bouisset F et al.* **Real-World Efficacy of Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors (PCSK9i) in Heterozygous Familial Hypercholesterolemia Patients Referred for Lipoprotein Apheresis**. Medical science monitor : international medical journal of experimental and clinical research 2021; 27:e928784.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33958572

ABSTRACT
BACKGROUND A small proportion of familial hypercholesterolemia (FH) patients can adequately control this condition, although achieving the recommended targets for low-density lipoprotein cholesterol (LDL-c) levels remains a challenge. Proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) are new and potent lipid-lowering drugs. However, there is scarce literature on real-world data about their use in patients with FH. MATERIAL AND METHODS We examined the reduction in LDL-c levels from the baseline, after PCSK9i initiation in heterozygous familial hypercholesterolemia patients referred for lipoprotein apheresis in our regional lipid clinic. The study was conducted from March 2018 to September 2019, the period immediately after PCSK9i reimbursement was available in France. PCSK9i was added on top of the patients' maximal tolerated lipid-lowering regimens. RESULTS The study had 123 patients with heterozygous FH. The mean age of the patients was 59±11 years. The mean baseline LDL-c for all the participants was 277±78 mg/dl. It was 283±81 mg/dl in the PCSK9i monotherapy group (n=83), 247±68 mg/dl in the PCSK9i plus ezetimibe group (n=12), and 264±78 mg/dl in the PCSK9i plus statin and ezetimibe group (n=28). The mean decrease observed in the LDL-c level from baseline was 136±70 mg/dl (n=123), 125±60 mg/dl (n=83), 103±77 mg/dl (n=12), and 175±70 mg/dl (n=28), respectively. CONCLUSIONS An overall reduction of 49.1% from the baseline LDL-c was observed in the heterozygous FH population after PCSK9i initiation in a real-world experience. The group treated with PCSK9i ezetimibe plus statin showed further reduction of their LDL-c levels with a better responder rate, achieving the target 50% reduction in LDL-c from the baseline.

[51] *Lucchi T*. **Dyslipidemia and prevention of atherosclerotic cardiovascular disease in the elderly**. Minerva medica 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33949178

ABSTRACT
The atherosclerotic cardiovascular disease (ASCVD) represents the leading cause of death and disability in the elderly. The study of atherosclerosis and the strategies to control ASCVD are evolving. All strategies emphasize the need to lower LDL cholesterol (LDL-C) through an appropriate lifestyle and the use of lipid-lowering drugs, mainly statins. Available evidence coming from clinical trials is useful to inform clinical choices but the older people are poorly represented in those trials. Thus evidence supporting the benefit of statin therapy for primary and secondary prevention of fatal and nonfatal ASCVD events in adults aged 75 years and older are limited. The pharmacological therapy of dyslipidemia is recommended by guidelines provided by international expert panels in adults, while in the elderly it is still a matter of debate. Statins are generally well tolerated drugs but their use in the elderly, especially in fragile ones or with multi-pathology that take many other drugs, requires a careful evaluation of the risk-benefit ratio and a shared decision-making process between doctor and patient.

[52] *Cesaro A, Riccio C, Calabrò P*. **Lipid-lowering therapy in high cardiovascular risk patients during COVID-19 pandemic: keep focused on the target**. Monaldi Arch Chest Dis 2021; 91.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33942600

ABSTRACT
To the Editor COVID-19 (COrona VIrus Disease) patients with cardiovascular (CV) disease, multiple CV risk factors or comorbidities (i.e., arterial hypertension and diabetes) were shown to be more

prone to a worse prognosis. SARS-CoV-2 is a still unknown enemy and the role of concomitant cardiovascular therapies has been controversial in the early stages, particularly with regard to Angiotensin-Converting Enzyme inhibitors...

[53] *Fahed AC, Jang IK*. **Plaque erosion and acute coronary syndromes: phenotype, molecular characteristics and future directions**. Nature reviews. Cardiology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33953381
ABSTRACT
Although acute coronary syndromes (ACS) remain one of the leading causes of death, the clinical presentation has changed over the past three decades with a decline in the incidence of ST-segment elevation myocardial infarction (STEMI) and an increase in non-STEMI. This epidemiological shift is at least partially explained by changes in plaque biology as a result of the widespread use of statins. Historically, atherosclerotic plaque rupture of the fibrous cap was thought to be the main culprit in ACS. However, plaque erosion with an intact fibrous cap is now responsible for about one third of ACS and up to two thirds of non-STEMI. Two major research approaches have enabled a better understanding of plaque erosion. First, advanced intravascular imaging has provided opportunities for an 'optical biopsy' and extensive phenotyping of coronary plaques in living patients. Second, basic science experiments have shed light on the unique molecular characteristics of plaque erosion. At present, patients with ACS are still uniformly treated with coronary stents irrespective of the underlying pathobiology. However, pilot studies indicate that patients with plaque erosion might be treated conservatively without coronary stenting. In this Review, we discuss the patient phenotype and the molecular characteristics in atherosclerotic plaque erosion and provide our vision for a potential major shift in the management of patients with plaque erosion.

[54] *Pereira TS, Fonseca FAH, Fonseca MIH et al.* **Phytosterol consumption and markers of subclinical atherosclerosis: Cross-sectional results from ELSA-Brasil**. Nutrition, metabolism, and cardiovascular diseases : NMCD 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33965299
ABSTRACT
BACKGROUND AND AIMS: Phytosterol (PS) consumption is associated with lower total and LDL-cholesterol (LDL-c) concentrations, but its impact on cardiovascular risk is unclear. This study assessed the effect of usual intake of PS on markers of subclinical atherosclerosis in the Longitudinal Study of Adult Health (ELSA-Brasil). METHODS AND RESULTS: This cross-sectional study included 2560 participants of ELSA-Brasil, aged 48 (43-54) years, with available food frequency questionnaires (FFQ), coronary artery calcium (CAC) scores, carotid intima media thickness (cIMT), and carotid-femoral pulse wave velocity (cf-PWV), at baseline. Several logistic and linear regression models were used, and significance level was set at a $P < 0.05$. Mean values (SD) for PS consumption were 256 (198) mg/day, CAC 22.78 (110.54) Agatston Units, cf-PWV 9.07 (1.60) m/s and cIMT 0.57 (0.12) mm. PS consumption in Q4 was associated with lower total- and LDL-c levels, and with higher percentiles of cf-PWV ($P < 0.001$). Proportion of subjects in Q4 of PS consumption was 1.5 times higher among individuals in cf-PWV Q4, than in Q1 ($P = 0.002$, for comparisons among quartiles). There was a trend ($P = 0.003$) for higher cf-PWV with higher PS intake. In crude logistic and linear regressions, PS intake was associated with cf-PWV. In the adjusted models, these associations disappeared. No associations were found between PS and cIMT or CAC.

CONCLUSIONS: In this large and apparently healthy cross-sectional sample from ELSA-Brasil, usual PS consumption was associated with lower total- and LDL-cholesterol, but not with markers of subclinical atherosclerosis.

[55] *Smetanina N, Valickas R, Vitkauskiene A et al.* **Prevalence of Metabolic Syndrome and Impaired Glucose Metabolism among 10- to 17-Year-Old Overweight and Obese Lithuanian Children and Adolescents**. Obes Facts 2021:1-12.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33951670
ABSTRACT
BACKGROUND: Overweight (Ow) and obesity among adults and children increases the risk of metabolic consequences. Metabolic syndrome (MS) and impaired glucose metabolism are well-known risk factors for cardiovascular diseases and type 2 diabetes. The aim of this study was to evaluate the prevalence of MS and impaired glucose metabolism among Ow and obese (Ob) children and adolescents (aged 10-17 years) in Lithuania, and to evaluate the associations between insulin resistance (IR) indices and anthropometric parameters as well as metabolic disturbances. METHODS: The study population consisted of 344 OwOb children and adolescents of all pubertal stages. Oral glucose tolerance tests (OGTTs), IR and β cell function indices, lipid profile, and anthropometric parameters of all subjects were analyzed. MS was defined according to the International Diabetes Federation consensus guidelines. RESULTS: MS was found in 21.3% of the OwOb children and adolescents, and 12.1% had impaired glucose metabolism (6.9% with impaired fasting glucose, 4.5% with impaired glucose tolerance, and 0.6% with type 2 diabetes). IR was directly related to body mass index and waist circumference, waist-to-height and waist-to-hip ratios, and sum of skin-fold thicknesses. Children with MS were more insulin-resistant, had higher odds ratio for prediabetes and had a more disturbed lipid profile than subjects without MS. Moreover, total cholesterol and low-density lipoprotein cholesterol levels were significantly lower in the more mature OwOb adolescents. CONCLUSION: MS and lipid profile disturbances are common in OwOb children and adolescents. MS is directly associated with IR. Therefore, OwOb children and adolescents should be carefully followed up for metabolic abnormalities during late childhood as these can persist into adulthood.

[56] *Aschenbrenner B, Negro G, Savic D et al.* **Simvastatin is effective in killing the radioresistant breast carcinoma cells**. Radiol Oncol 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33939900
ABSTRACT
BACKGROUND: Statins, small molecular 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, are widely used to lower cholesterol levels in lipid-metabolism disorders. Recent preclinical and clinical studies have shown that statins exert beneficial effects in the management of breast cancer by increasing recurrence free survival. Unfortunately, the underlying mechanisms remain elusive. MATERIALS AND METHODS: Simvastatin, one of the most widely prescribed lipophilic statins was utilized to investigate potential radiosensitizing effects and an impact on cell survival and migration in radioresistant breast cancer cell lines. RESULTS: Compared to parental cell counterparts, radioresistant MDA-MB-231-RR, T47D-RR andAu565-RR cells were characterized by upregulation of 3-hydroxy-3-methylglutharyl-coenzyme A reductase (HMGCR) expression accompanied by epithelial-to-mesenchymal transition (EMT) activation. Radioresistant breast cancer

cells can be killed by simvastatin via mobilizing of a variety of pathways involved in apoptosis and autophagy. In the presence of simvastatin migratory abilities and vimentin expression is diminished while E-cadherin expression is increased. CONCLUSIONS: The present study suggests that simvastatin may effectively eradicate radioresistant breast carcinoma cells and diminish their mesenchymal phenotypes.

[57] *Leiner T*. **A New Era in Atherosclerotic Plaque Characterization with Photon-counting CT**. Radiology 2021:210313.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33949896
ABSTRACT

[58] *Tripaldi R, Lanuti P, Simeone PG et al.* **Endogenous PCSK9 may influence circulating CD45(neg)/CD34(bright) and CD45(neg)/CD34(bright)/CD146(neg) cells in patients with type 2 diabetes mellitus**. Scientific reports 2021; 11:9659.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33958634
ABSTRACT
Protease proprotein convertase subtilisin/kexin type 9 (PCSK9) is a regulator of LDL cholesterol clearance and has been associated with cardiovascular risk. PCSK9 inhibitors increase in vivo circulating endothelial progenitor cells (EPCs), a subtype of immature cells involved in ongoing endothelial repair. We hypothesized that the effect of PCSK9 on vascular homeostasis may be mediated by EPCs in patients with or without type 2 diabetes mellitus (T2DM). Eighty-two patients (45 with, 37 without T2DM) at high cardiovascular risk were enrolled in this observational study. Statin treatment was associated with higher circulating levels of PCSK9 in patients with and without T2DM ($p<0.001$ and $p=0.036$) and with reduced CD45(neg)/CD34(bright) (total EPC compartment) ($p=0.016$) and CD45(neg)/CD34(bright)/CD146(neg) (early EPC) ($p=0.040$) only among patients with T2DM. In the whole group of patients, statin treatment was the only independent predictor of low number of CD45(neg)/CD34(bright) ($\beta=-0.230$; $p=0.038$, adjusted $R(2)=0.041$). Among T2DM patients, PCSK9 circulating levels were inversely related and predicted both the number of CD45(neg)/CD34(bright) ($\beta=-0.438$; $p=0.003$, adjusted $R(2)=0.173$), and CD45(neg)/CD34(bright)/CD146(neg) ($\beta=-0.458$; $p=0.002$, adjusted $R(2)=0.191$) independently of age, gender, BMI and statin treatment. In high-risk T2DM patients, high endogenous levels of PCSK9 may have a detrimental effect on EPCs by reducing the endothelial repair and worsening the progression of atherothrombosis.

[59] Pirahanchi Y, Anoruo M, Sharma S. Biochemistry, Lipoprotein Lipase. In: StatPearls. Treasure Island (FL): StatPearls Publishing
 2021.
[60] *Hackam DG*. **Optimal Medical Management of Asymptomatic Carotid Stenosis**. Stroke 2021; 52:2191-2198.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33947208
ABSTRACT
Asymptomatic carotid stenosis (ACS) due to atherosclerosis is a risk factor for ipsilateral ischemic cerebrovascular events and cognitive impairment. The prognosis of ACS has improved over the past 4 decades due largely to improvements in medical management. Most patients with ACS can be

managed without revascularization, but some patients with vulnerable plaque should be considered for revascularization. Regardless of the decision to refer for revascularization, all patients with ACS should receive intensive medical management. This includes lifestyle modification (Mediterranean diet, exercise, and smoking cessation) and pharmacological therapy (antiplatelets, lipid-lowering agents, blood pressure reduction, and glycemic control). Patients with ACS often have atherosclerosis in other critical locations, and thus optimal medical therapy is likely to reduce events outside the carotid arteries. The nature of optimal medical therapy is described.

[61] *Nagayama D, Saiki A, Shirai K*. **The Anti-Cancer Effect of Pitavastatin May Be a Drug-Specific Effect: Subgroup Analysis of the TOHO-LIP Study**. Vascular health and risk management 2021; 17:169-173.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33953560
ABSTRACT
The significance of statin treatment for the reduction of cardiovascular (CV) disease has been reported, whereas other reports have also described anti-cancer properties associated with the class effect of statins. However, the differences in anti-cancer effect of various types of statins have rarely been examined. Pitavastatin is a statin with a different chemical structure and pharmacokinetics from other statins, and the mechanism of the specific anti-cancer effect of pitavastatin has been reported in in vivo therapeutic models. We previously revealed that pitavastatin therapy was superior to atorvastatin therapy in the prevention of CV events, despite similar LDL-cholesterol-lowering effect in the TOHO Lipid Intervention Trial Using Pitavastatin (TOHO-LIP). Furthermore, in subgroup analysis of the TOHO-LIP study, cumulative 240-week incidence of new cancer cases tended to be lower in the pitavastatin group compared to the atorvastatin group [0.32% (1/312) vs 1.94% (6/310), log-rank P=0.051]. This finding might reveal the superiority of pitavastatin to prevent carcinogenesis. The molecular mechanism by which pitavastatin suppresses the incidence of any-organ cancer is gradually elucidated, and new combination of cancer treatments with pitavastatin will be developed in the future to further enhance the anti-cancer activity and reduce the side effects.

[62] *Akimoto H, Takahashi Y, Asai S*. **[Effects of Fibrates on Risk of Development of Diabetic Retinopathy in Japanese Working Age Patients with Type 2 Diabetes and Dyslipidemia: a Retrospective Cohort Study]**. Yakugaku Zasshi 2021; 141:761-769.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33952760
ABSTRACT
The aims of the present study were to investigate the effects of fenofibrate and bezafibrate on the risk of development of diabetic retinopathy (DR) in patients with type 2 diabetes and dyslipidemia. Japanese working age patients with type 2 diabetes and dyslipidemia were extracted from the Nihon University School of Medicine Clinical Data Warehouse. These patients were divided into three groups: control group (n=2549), fenofibrate group (n=40), and bezafibrate group (n=135). Multivariate logistic regression analysis was performed to assess the association between fibrates and the development of DR. After adjustment for covariates, fenofibrate showed no association with the risk of DR [adjusted odds ratio (OR), 0.160; 95% CI, 0.021-1.209; p=0.0758]. Bezafibrate also showed no association with the risk of DR (adjusted OR, 0.731; 95% CI, 0.411-1.299; p=0.2855). However, poor control of hemoglobin A1c (HbA1c ≥8.0%; adjusted OR, 3.623; 95% CI, 2.649-4.956; p<0.0001) and high low-density lipoprotein cholesterol (LDL-C ≥140 mg/dL; adjusted OR, 1.399; 95% CI, 1.013-

1.932; p=0.0415) within the follow-up period of type 2 diabetes and dyslipidemia increased the risk of DR. Our results suggested that to prevent development of DR in patients with type 2 diabetes and dyslipidemia, controlling LDL-C levels as well as HbA1c levels under coexistence type 2 diabetes and dyslipidemia is more important than the selection of fibrate.