[1] *Sun J, Kumar Panda P, Kumar Samal S et al.* **Effects of Atorvastatin on T-Cell Activation and Apoptosis in Systemic Lupus Erythematosus and Novel Simulated Interactions With C-Reactive Protein and Interleukin 6**. ACR Open Rheumatol 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34302321

ABSTRACT

OBJECTIVE: We study activation of T helper 17 (Th17) and regulatory T (Treg) cells and induction of apoptosis in cells from patients with systemic lupus erythematosus (SLE) compared with controls and effects of atorvastatin and its simulated interactions with other compounds. METHODS: Mononuclear cells from 10 patients with SLE and 10 controls were cultured in conditions that induce Th17 and/or Treg cell polarization and/or apoptosis and were studied by FACScan. Gene expression was determined by quantitative real-time reverse transcription-polymerase chain reaction. Cytokines in plasma were determined by enzyme-linked immunosorbent assay. The Search Tool for Interactions of Chemicals (STITCH) was used to retrieve information regarding the binding properties of atorvastatin. RESULTS: Among patients with SLE, the proportion of Th17 (CD4(+) IL17(+)) cells was higher compared with controls after activation, with Th17 or Treg polarizing cytokines, phorbol myristate acetate, and ionomycin. In contrast, Treg cells (CD4(+) CD25(+) CD127(dim/-)) frequencies were lower. CD95 stimulation induced relatively more apoptosis in Treg cells and less in Th17 cells, as compared with controls. Addition of atorvastatin normalized Th17/Treg cell balance and apoptosis induction. Accordingly, the ratio of RORC/FoxP3 decreased in patients with SLE. Interleukin 17 and interleukin 6 (IL-6) levels were increased in patients with SLE. Atorvastatin interacted strongly with C-reactive protein (CRP) and also significantly with IL-6. CONCLUSION: There is a higher proportion of Th17 cells and a lower proportion of Treg cells in patients with SLE after activation. Th17 cells were more resistant than Treg cells to CD95-induced apoptosis in SLE. Atorvastatin normalized these effects. Our findings reveal a novel mechanism behind the imbalance of Th17/Treg cells with implications for treatment in SLE. We determine for the first time simulated interaction between atorvastatin, CRP, and IL-6, implying a novel role of atorvastatin.

[2] *Pintarić H, Knezović Florijan M, Bridges I et al.* **Management of Hyperlipidemia in Very High and Extreme Risk Patients in Croatia: an observational study of treatment patterns and lipid control**. Acta clinica Croatica 2020; 59:641-649.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34285435

ABSTRACT

Our observational study evaluated current management of elevated low-density lipoprotein cholesterol (LDL-C) in adult secondary prevention patients (all very high risk (VHR) by European guidelines) attending specialist clinics across Croatia. Data were collected retrospectively from patient records for the preceding 12 months. The subset judged to be at extreme risk (ER; American Association of Clinical Endocrinologists (AACE) criteria; n=48) were compared with the remaining patients (VHR group; n=41). All patients were receiving statins (75.6% VHR/81.3% ER at high-intensity), with only a minority receiving concomitant lipid-lowering treatment (7.3% VHR/16.7% ER). Median (Q1, Q3) LDL-C levels at the last visit were 1.9 (1.6, 2.4) mmol/L for VHR and 2.1 (1.5, 3.1) mmol/L for ER, with only 41.5% (95% CI 26.3-57.9) of VHR patients and 27.1% (15.3-41.9) of ER patients attaining their LDL-C targets (<1.8 mmol/L and <1.42 mmol/L, respectively). Thus, we found that a substantial proportion of VHR and ER secondary prevention patients being treated across Croatia had LDL-C levels exceeding the targets recommended in the European and newer AACE

guidelines, but not all were receiving high-intensity statins. Identification of ER patients and their lipid patterns may help optimize usage of high-intensity statin treatment, alone or along with newer treatments, for better control of elevated LDL-C.

[3] *Vahedian-Azimi A, Rahimibashar F, Najafi A et al.* **Associastion of In-hospital Use of Statins, Aspirin, and Renin-Angiotensin-Aldosterone Inhibitors with Mortality and ICU Admission Due to COVID-19**. Advances in experimental medicine and biology 2021; 1327:205-214.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34279841
ABSTRACT
The exaggerated host response to Sars-CoV-2 plays an important role in COVID-19 pathology but provides a therapeutic opportunity until definitive virus targeted therapies and vaccines become available. Given a central role of endothelial dysfunction and systemic inflammation, repurposing ACE inhibitors (ACEIs), angiotensin receptor blockers (ARBs), statins, and aspirin has been of interest. In this retrospective, single-center study, we evaluated the primary outcomes of mortality and ICU admission in 587 hospitalized patients with documented COVID-19 with or without ACEIs, ARBs, statins, and aspirin. Atorvastatin was associated with reduced mortality, which persisted after adjusting for age, lockdown status, and other medications (OR: 0.18. 95% CI: 0.06-0.49, P = 0.001). ACEIs were also associated with reduced mortality in the crude model (OR: 0.20, CI: 0.06-0.66, P = 0.008), as ACEIs and ARBs were combined as a single group (OR: 0.35, CI: 0.16-0.75, P = 0.007), although ARBs alone did not reach statistical significance. There was no association between any medications and risk of ICU admission. Aspirin only achieved a significant association of reduced mortality in a subgroup of patients with diabetes in the crude model (OR: 0.17, CI: 0.04-0.80, P = 0.02). The reduced mortality observed with atorvastatin is consistent with other literature, and consideration should be given to atorvastatin as a COVID-19 treatment. While there was suggested benefit of ACEIs and ARBs in the present study, other studies are varied and further studies are warranted to recommend employing these medications as a treatment strategy. Nevertheless, this study combined with others continues to give credibility that ACEIs and ARBs are safe to continue in the setting of COVID-19.

[4] *Merli GJ, Weitz HH*. **Annals Consult Guys - Lipid-Lowering Therapy in Patients of Advanced Age**. Annals of internal medicine 2021; 174:Cg1.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34280337
ABSTRACT

[5] *Janik MJ, Urbach DV, van Nieuwenhuizen E et al.* **Alirocumab treatment and neurocognitive function according to the CANTAB scale in patients at increased cardiovascular risk: A prospective, randomized, placebo-controlled study**. Atherosclerosis 2021; 331:20-27.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34303265
ABSTRACT
BACKGROUND AND AIMS: Trials of the fully human monoclonal antibody proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9) alirocumab in hypercholesterolemia demonstrated substantial low-density lipoprotein cholesterol (LDL-C) lowering, reduction in cardiovascular (CV) events and outcomes, and a generally acceptable safety and tolerability profile. The impact of maintaining low LDL-C levels on higher order brain function is unclear, with reports of neurocognitive disorders with

other lipid-lowering therapies. METHODS: Patients (n = 2176) with heterozygous familial hypercholesterolemia (HeFH) or non-FH, at high or very-high CV risk despite maximally tolerated statin therapy, randomly received subcutaneous alirocumab 75/150 mg or placebo every 2 weeks in this double-blind, placebo-controlled trial. The primary outcome was prospectively evaluated every 24 weeks over 96 weeks by Cambridge Neuropsychological Test Automated Battery (CANTAB). RESULTS: Among 2086 patients with CANTAB cognitive domain Spatial Working Memory Strategy (SWMS) assessments, change from baseline to Week 96 in SWMS z-score (primary outcome) achieved noninferiority between alirocumab and placebo (least squares [LS] mean change at Week 96, -0.180 vs -0.200; LS mean difference vs placebo [95% confidence interval]: -0.020 [-0.094 to 0.055], p = 0.6055). Exploratory outcome measures, which further assessed neurocognitive function in the CANTAB domains, did not differ significantly over 96 weeks and achieved nominal noninferiority between treatment groups. Alirocumab resulted in nominally significant reductions in LDL-C and other lipid parameters, and was generally well tolerated. CONCLUSIONS: Confirming previous PCSK9 inhibitor data, alirocumab showed no effect on neurocognitive function over 96 weeks' treatment, substantially reduced LDL-C and was generally well tolerated in patients with HeFH or non-FH at high or very-high CV risk.

[6] *Taloyan M, Kia M, Lamian F et al.* **Web-based support for individuals with type 2 diabetes - a feasibility study**. BMC Health Serv Res 2021; 21:721.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34294112
ABSTRACT
BACKGROUND: Self-care is one of the cornerstones in the treatment of type 2 diabetes. Patients with type 2 diabetes struggle to maintain acceptable levels of blood sugar, blood pressure and lipids, the fundamental for the prevention of macro- and microvascular as well as neuropathic complications. The primary aim of the study was to evaluate the feasibility and describe patients' and caregivers' experiences of using the web- and smartphone-based system Triabetes. The secondary aim was to investigate if the use of the system could improve patients' clinical outcomes. METHODS: Feasibility was assessed with describing recruitment rate and the participant´s views of using the system. Laboratory and anthropometry data were also collected. RESULTS: The study showed that recruitment of patients to participate in the intervention was limited and compliance to the study protocol was low. A majority of the patients stated that the system was easy to get an overview of and that the system motivated them and made it easier and fun to handle lifestyle habits. A secondary finding of the study was that there was a significant lowering of LDL values. CONCLUSIONS: Feasibility in terms of recruitment rate was low. The participants agreed that the application overall was useful but suggested several improvements. Summarized lessons learned from this study are following: (1) we need more knowledge about what motivates a person to use a digital tool for a longer period of time; (2) the tool must be easy and less time consuming to use; (3) the technical structure needs to be improved and automatic recording of data must be improved.

[7] *Karimi E, Yarizadeh H, Setayesh L et al.* **High carbohydrate intakes may predict more inflammatory status than high fat intakes in pre-menopause women with overweight or obesity: a cross-sectional study**. BMC research notes 2021; 14:279.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34289902
ABSTRACT

OBJECTIVE: The associations between dietary carbohydrate, fat intake, and inflammation are controversial. Most existing data are from industrialized societies which low-carbohydrate and high-fat diet is common and so their attribution to other populations remains unclear. We evaluated the association of fat and carbohydrate intakes with inflammatory markers in pre-menopause women with overweight or obesity in Iran. RESULTS: Three hundred and sixty women with body mass index (BMI) ≥25 were included to this study. The levels of monocyte chemoattractant protein-1 (MCP-1) indicated a trend towards significance across tertiles of total dietary carbohydrate. We found that the levels of galectin-3 were negatively associated with dietary carbohydrate in adjusted model. In addition, the levels of MCP-1 and transforming growth factor beta (TGF-β) were positively correlated to dietary carbohydrate. No significant relationship was demonstrated between inflammatory parameters and total fat intake). However, there was a borderline significant negative association between total fat intake and TGF-β level in adjusted model. Therefore, a total dietary carbohydrate were related to elevated inflammation risk, while a total fat intake were not associated to higher inflammation. This study suggests reconsideration of applying global dietary guidelines in societies with high carbohydrate diet.

[8] *Abudalou M, Mohamed AS, Vega EA, Al Sbihi A*. **Colchicine-induced rhabdomyolysis: a review of 83 cases**. BMJ case reports 2021; 14.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34290008
ABSTRACT
A 74-year-old man with medical history significant for atrial fibrillation, hyperlipidaemia and coronary artery disease on atorvastatin presented to the emergency department with profound weakness. The patient reports he first noticed his weakness 4 weeks after starting colchicine, prescribed for recurrent pericarditis with pericardial effusion, a complication following recent coronary artery bypass grafting. The patient was also on prednisone therapy for presumed post-pericardiotomy syndrome. The weakness involved all four limbs but was more notable in the lower extremities, with preserved sensation and tenderness to palpation. Labs showed an elevated creatinine phosphokinase and serum creatinine consistent with rhabdomyolysis. Discontinuation of the offending medications, including colchicine and atorvastatin, as well as intravenous fluid resuscitation with physical rehabilitation, led to improvement in the patient's symptoms. He was eventually discharged to a rehabilitation facility to continue physical therapy.

[9] *Ali AS*. **Insulin can be used to treat severe hypertriglyceridaemia in pregnant women without diabetes**. BMJ case reports 2021; 14.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34290025
ABSTRACT
Severe hypertriglyceridaemia can lead to acute pancreatitis, which is associated with maternal and perinatal mortality when it occurs in pregnancy. Rapid reduction of triglyceride levels is a primary goal in the management of severe hypertriglyceridaemia, however, there are limited safe option for treatment in pregnancy. We present a case of a woman without diabetes presenting with severe hypertriglyceridaemia in late gestation who was safely and successfully treated with insulin and review the literature surrounding the management of this important condition.

[10] *Kambic T, Šarabon N, Hadžić V, Lainscak M*. **Effects of high-load and low-load resistance training in patients with coronary artery disease: rationale and design of a randomised controlled clinical trial**. BMJ open 2021; 11:e051325.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34301669

ABSTRACT
INTRODUCTION: Resistance training (RT) combined with aerobic training (AT) enhances the effects of cardiac rehabilitation (CR) in patients with coronary artery disease (CAD). However, it remains to be investigated which type of RT (high loads (HLs) vs low loads (LLs)) is more efficacious in improving exercise performance, cardio-metabolic health and quality of life. METHODS AND ANALYSIS: A randomised, controlled, clinical trial will enrol 20 patients with CAD into each of three study arms (total 60 patients): HL-RT (70%-80% of one repetition maximum (1-RM)) combined with AT; LL-RT (30%-40% of 1-RM) combined with AT and AT alone as standard care. Primary outcomes (maximal aerobic capacity, maximal leg isometric strength) will be assessed at baseline and after 36 training sessions. Other outcomes will include acute haemodynamic responses to LL-RT and HL-RT, body composition, physical performance, blood biomarkers (lipids, glucose metabolism, inflammation, growth factors), physical activity and quality of life. The intention-to-treat principle will be used to analyse the data. ETHICS AND DISSEMINATION: The study design and protocol have been approved by the National Medical Ethics Committee of Slovenia (registration number: 0120-573/2019/15). The study will be conducted in accordance with the Declaration of Helsinki. The results of the study will be published as peer-reviewed manuscripts and congress presentations, communicated with patients and the clinical community, and shared through posts on social media. The findings of the study will be disseminated among the national CR clinical community (CR centres, Slovenian association of coronary clubs) with active participation of the patients enrolled in the study. This study will expand our knowledge of RT in combination with AT in CR. We expect to find different effects of HL-RT versus LL-RT, with implications for RT strategies in rehabilitation of patients with CAD. TRIAL REGISTRATION NUMBER: NCT04638764.

[11] *Farrington L, Mortimore G*. **Chronic limb ischaemia: case study and clinical literature review**. Br J Nurs 2021; 30:846-851.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34288743

ABSTRACT
This article will discuss chronic limb ischaemia as the result of peripheral artery disease (PAD) using a case study. The patient's concurrent diagnosis of metastases meant clinical decision making was complex and treatment options were limited. PAD is the third most common clinical presentation of atherosclerosis after coronary artery disease and stroke. Although advances in radiological technology and biochemical screening offer the potential for earlier intervention and improved survival rates for patients with PAD, a review of the evidence suggests that commitment to more conservative approaches, such as exercise therapy and health promotion, could have more sustainable, longer-term benefits for patients with chronic limb ischaemia. The therapeutic nature of the nurse-patient relationship makes nurses ideally placed for encouraging lifestyle changes and signposting to support services. Active participation from the patient is imperative for any potential modifications, which should be individualised as part of a holistic care plan, to ensure patient engagement and compliance. Therefore emphasis should remain on the management and prevention of modifiable risk factors, for which the nurse's role is an integral part to ensure success.

[12] *Sander P, Feng M, Schweitzer MK et al.* **Approved drugs ezetimibe and disulfiram enhance mitochondrial Ca(2+) uptake and suppress cardiac arrhythmogenesis**. Br J Pharmacol 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34287836
ABSTRACT
BACKGROUND AND PURPOSE: Treatment of cardiac arrhythmia remains challenging due to severe side effects of common anti-arrhythmic drugs. We previously demonstrated that mitochondrial Ca(2+) uptake in cardiomyocytes represents a promising new candidate structure for safer drug therapy. However, druggable agonists of mitochondrial Ca(2+) uptake suitable for preclinical and clinical studies are still missing. EXPERIMENTAL APPROACH: Herewe screened 727 compounds with a history of use in human clinical trials in a three-step screening approach. As a primary screening platform we used a permeabilized HeLa cell-based mitochondrial Ca(2+) uptake assay. Hits were validated in cultured HL-1 cardiomyocytes and finally tested for anti-arrhythmic efficacy in three translational models: a Ca(2+) overload zebrafish model and cardiomyocytes of both a mouse model for catecholaminergic polymorphic ventricular tachycardia (CPVT) and induced pluripotent stem cell derived cardiomyocytes from a CPVT patient. KEY RESULTS: We identifiedtwo candidate compounds, the clinically approved drugs ezetimibe and disulfiram, which stimulate SR-mitochondria Ca(2+) transfer at nanomolar concentrations. This is significantly lower compared to the previously described mitochondrial Ca(2+) uptake enhancers (MiCUps) efsevin, a gating modifier of the voltage-dependent anion channel 2, and kaempferol, an agonist of the mitochondrial Ca(2+) uniporter. Both substances restored rhythmic cardiac contractions in a zebrafish cardiac arrhythmia model and significantly suppressed arrhythmogenesis in freshly isolated ventricular cardiomyocytes from a CPVT mouse model as well as induced pluripotent stem cell derived cardiomyocytes from a CPVT patient. CONCLUSION AND IMPLICATIONS: Taken together we identified ezetimibe and disulfiram as novel MiCUps and efficient suppressors of arrhythmogenesis and as such as, promising candidates for future preclinical and clinical studies.

[13] *Marston NA, Oyama K, Jarolim P et al.* **Combining High-Sensitivity Troponin With the American Heart Association/American College of Cardiology Cholesterol Guidelines to Guide Evolocumab Therapy**. Circulation 2021; 144:249-251.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34279993
ABSTRACT

[14] *Murtola TJ, Siltari A*. **Statins for Prostate Cancer: When and How Much?** Clin Cancer Res 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34281913
ABSTRACT
Statins have plausible biological effects against prostate cancer cells and are associated with improved disease-specific mortality. In current randomized placebo-controlled trial, low-dose atorvastatin caused no difference in relapses after radical prostatectomy in Asian men. Future trials should study higher statin doses at later disease stages with survival as the endpoint.See related article by Jeong et al., p. 5004.

[15] *Di Taranto MD, Giacobbe C, Palma D et al.* **Genetic spectrum of familial hypercholesterolemia and correlations with clinical expression: Implications for diagnosis improvement**. Clinical genetics 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34297352

ABSTRACT
Familial hypercholesterolemia (FH) is the most common genetic disease caused by variants in LDLR, APOB, PCSK9 genes; it is characterized by high levels of LDL-cholesterol and premature cardiovascular disease. We aim to perform a retrospective analysis of a genetically screened population (528 unrelated patients-342 adults and 186 children) to evaluate the biochemical and clinical correlations with the different genetic statuses. Genetic screening was performed by traditional sequencing and some patients were re-analyzed by next-generation-sequencing. Pathogenic variants, mainly missense in the LDLR gene, were identified in 402/528 patients (76.1%), including 4 homozygotes, 17 compound heterozygotes and 1 double heterozygotes. A gradual increase of LDL-cholesterol was observed from patients without pathogenic variants to patients with a defective variant, to patients with a null variant and to patients with two variants. Six variants accounted for 51% of patients; a large variability of LDL-cholesterol was observed among patients carrying the same variant. The frequency of pathogenic variants gradually increased from unlikely FH to definite FH, according to the Dutch Lipid Clinic Network criteria. Genetic diagnosis can help prognostic evaluation of FH patients, discriminating between the different genetic statuses or variant types. Clinical suspicion of FH should be considered even if few symptoms are present or if LDL-cholesterol is only mildly increased.

[16] *Mohamed I, Kamarizan MFA, Da Silva A*. **Medical adjuvant treatment to increase patency of arteriovenous fistulae and grafts**. The Cochrane database of systematic reviews 2021; 7:Cd002786.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34298589

ABSTRACT
BACKGROUND: People with end-stage renal disease (ESRD) often require either the formation of an arteriovenous fistula (AVF) or an interposition prosthetic arteriovenous graft (AVG) for haemodialysis. These access sites should ideally have a long life and a low rate of complications (e.g. thrombosis, infection, stenosis, aneurysm formation and distal limb ischaemia). Although some of the complications may be unavoidable, any adjuvant technique or medical treatment aimed at decreasing complications would be welcome. This is the fourth update of the review first published in 2003. OBJECTIVES: To assess the effects of adjuvant drug treatment in people with ESRD on haemodialysis via autologous AVFs or prosthetic interposition AVGs. SEARCH METHODS: The Cochrane Vascular Information Specialist searched the Cochrane Vascular Specialised Register, CENTRAL, MEDLINE, Embase and CINAHL databases and ClinicalTrials.gov trials register to 6 August 2020. SELECTION CRITERIA: Randomised controlled trials of active drug versus placebo in people with ESRD undergoing haemodialysis via an AVF or prosthetic interposition AVG. DATA COLLECTION AND ANALYSIS: For this update, two review authors (IM, MFAK) independently selected trials for inclusion, extracted data, assessed risk of bias and assessed the certainty of the evidence according to GRADE. We resolved disagreements by discussion or consultation with another review author (ADS). The primary outcome was the long-term fistula or graft patency rate. Secondary outcomes included duration of hospital stay; complications such as infection, aneurysm

formation, stenosis and distal limb ischaemia; and number of related surgical or radiological interventions. MAIN RESULTS: For this update, one additional study was suitable for inclusion, making a total of 13 trials with 2080 participants. Overall the certainty of the evidence was low or moderate due to short follow-up periods, heterogeneity between trials, small sample sizes, and risk of bias due to incomplete reporting. Medical adjuvant treatments used in the included trials were aspirin, ticlopidine, dipyridamole, dipyridamole plus aspirin, warfarin, fish oil, clopidogrel, sulphinpyrazone and glyceryl trinitrate (GTN) patch. All included studies reported on graft patency by measuring graft thrombosis. There was insufficient evidence to determine if there was a difference in graft patency in studies comparing aspirin versus placebo (odds ratio (OR) 0.40, 95% confidence interval (CI) 0.07 to 2.25; 3 studies, 175 participants; low-certainty evidence). The meta-analysis for graft patency comparing ticlopidine versus placebo favoured ticlopidine (OR 0.45, 95% CI 0.25 to 0.82; 3 studies, 339 participants; moderate-certainty evidence). There was insufficient evidence to determine if there was a difference in graft patency in studies comparing fish oil versus placebo (OR 0.24, 95% CI 0.03 to 1.95; 2 studies, 220 participants; low-certainty evidence); and studies comparing clopidogrel and placebo (OR 0.40, 95% CI 0.13 to 1.19; 2 studies, 959 participants; moderate-certainty evidence). Similarly, there was insufficient evidence to determine if there was a difference in graft patency comparing the effect of dipyridamole versus placebo (OR 0.46, 95% CI 0.11 to 1.94; 1 study, 42 participants, moderate-certainty evidence) and dipyridamole plus aspirin versus placebo (OR 0.64, CI 0.16 to 2.56; 1 study, 41 participants; moderate-certainty evidence); comparing low-intensity warfarin with placebo (OR 1.76, 95% CI 0.78 to 3.99; 1 study, 107 participants; low-certainty evidence); comparing sulphinpyrazone versus placebo (OR 0.43, 95% CI 0.03 to 5.98; 1 study, 16 participants; low-certainty evidence) and comparing GTN patch and placebo (OR 1.26, 95% CI 0.63 to 2.54; 1 study, 167 participants; moderate-certainty evidence). The single trial evaluating warfarin was terminated early because of major bleeding events in the warfarin group. Only two studies published data on the secondary outcome of related interventions (surgical or radiological); there was insufficient evidence to determine if there was a difference in related interventions between placebo and treatment groups. None of the included studies reported on the duration of hospital stay. Most studies reported complications ranging from mortality to nausea. However, data on complications were limited and reporting varied between studies. AUTHORS' CONCLUSIONS: The meta-analyses of three studies for ticlopidine (an antiplatelet treatment), which all used the same dose of treatment but with a short follow-up of only one month, suggest ticlopidine may have a beneficial effect as an adjuvant treatment to increase the patency of AVFs and AVGs in the short term. There was insufficient evidence to determine if there was a difference in graft patency between placebo and other treatments such as aspirin, fish oil, clopidogrel, dipyridamole, dipyridamole plus aspirin, warfarin, sulphinpyrazone and GTN patch. The certainty of the evidence was low to moderate due to short follow-up periods, the small number of studies for each comparison, small sample sizes, heterogeneity between trials and risk of bias due to incomplete reporting. Therefore, it appears reasonable to suggest further prospective studies be undertaken to assess the use of these antiplatelet drugs in renal patients with an AVF or AVG.

[17] *Hu J, Yang C, Yang G et al.* **Effects of atorvastatin doses on serum level of procalcitonin and predictors for major adverse cardiovascular events in patients with acute myocardial infarction: a pilot study and post hoc analysis**. Coronary artery disease 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34292180

ABSTRACT
BACKGROUND: Inflammation plays an important role in acute myocardial infarction (AMI). Procalcitonin levels rise in response to proinflammatory stimuli. This study aimed to investigate the effects of different doses of atorvastatin on the serum inflammatory profiles, especially procalcitonin and major adverse cardiovascular events (MACEs) in patients with AMI during hospitalization. METHODS: The patients who were admitted to the Coronary Care Unit of The Third Medical Center of PLA General Hospital (Beijing, China) between January 2015 and December 2015 with a diagnosis of AMI were enrolled, and randomized to atorvastatin 20 mg/day postoperatively (20-mg group), 40 mg/day postoperatively (40-mg group) and 80 mg preoperatively+40 mg/day postoperatively (80/40-mg group). Serum procalcitonin and high-sensitivity C-reactive protein (hs-CRP) were evaluated before and at 1 and 3 days after percutaneous coronary intervention (PCI). RESULTS: A total of 112 patients with AMI (23 women and 89 men) were prospectively eligible for the study. There were no significant differences in most clinical data among the three groups. The 80/40-mg group showed significantly reduced serum procalcitonin levels at 1 and 3 days after PCI ($P<0.001$) and reduced hs-CRP levels at 3 days $P=0.001$) compared with 20-mg and 40-mg groups. Serum procalcitonin (OR, 4.593; 95% CI, 1.476-8.387; $P=0.005$), hs-CRP (OR, 1.149; 95% CI, 1.012-1.338; $P=0.018$), highly sensitive cardiac troponin T (OR, 1.255; 95% CI, 1.004-1.569, $P=0.009$) and Gensini score (OR, 1.022; 95% CI, 1.045-1.062; $P=0.013$) were independently associated with MACEs during hospitalization. CONCLUSION: The use of atorvastatin 80 mg before and 40 mg/day after PCI in patients with AMI can effectively reduce serum inflammatory factors. procalcitonin and hs-CRP were independently associated with in-hospital MACEs.

[18] *Sekhar A, Kuttan A, Borges JC, Rajachandran M*. **Food for Thought or Feeding a Dogma? Diet and Coronary Artery Disease: a Clinician's Perspective**. Current cardiology reports 2021; 23:127.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34279741

ABSTRACT
PURPOSE OF REVIEW: To provide an overview of nutrition studies evaluating the association of dietary saturated fat and meat intake with the development of coronary artery disease (CAD) and discuss implications of recent data. RECENT FINDINGS: Recent studies have led to the re-evaluation of the role of saturated fat in CAD. Randomized controlled trials (RCTs) support Mediterranean diet to reduce cardiovascular risk. Recent data revealed significant association of intake of meat or poultry with increased risk, but fish consumption was associated with lower risk of incident CAD. In this review, we provide a brief overview of the studies and data that have led to the re-evaluation of the link between saturated fat and CAD. Due to conflicting data from long-term prospective cohort studies and significant heterogeneity, associations of unprocessed meat with CAD are less clear compared to the role of processed meat. Pooled data from prospective cohort studies have overcome some of these limitations and show association of both processed and unprocessed meat and poultry intake but not fish consumption with incident CAD. These findings were also validated recently in a large UK Biobank prospective study. While recognizing the limitations of these cohort studies, we discuss relevant landmark RCTs. We finally consider the challenges with RCTs in nutrition research to improve the quality of evidence and need for evidence-based dietary guidelines with respect to saturated fat intake from a clinical perspective.

[19] *Tufail S, Siddique MI, Sarfraz M et al.* **Simvastatin nanoparticles loaded polymeric film as a potential strategy for diabetic wound healing: in vitro and in vivo evaluation**. Current drug delivery 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34288836
ABSTRACT
INTRODUCTION: The pleiotropic effects of statins are recently explored for wound healing through angiogenesis and lymph-angiogenesis that could be of great importance in diabetic wounds. AIM: Aim of the present study is to fabricate nanofilm embedded with simvastatin loaded chitosan nanoparticles (CS-SIM-NPs) has been reported herein to explore the efficacy of SIM in diabetic wound healing. METHODS: The NPs, prepared via ionic gelation, were 173nm ± 2.645 in size with a zeta potential -0.299 ± 0.009 and PDI 0.051 ± 0.088 with excellent encapsulation efficiency (99.97%). The optimized formulation (CS: TPP, 1:1) that exhibited the highest drug release (91.64%) was incorporated into polymeric nanofilm (HPMC, Sodium alginate, PVA), followed by in vitro characterization. The optimized nanofilm was applied to the wound created on the back of diabetes-induced (with alloxan injection 120 mg/kg) albino rats. RESULTS: The results showed significant ($p < 0.05$) improvement in the wound healing process compared to the diabetes-induced non-treated group. The results highlighted the importance of nanofilms loaded with SIM-NPs in diabetic wound healing through angiogenesis promotion at the wound site. CONCLUSION: Thus, CS-SIM-NPs loaded polymeric nanofilms could be an emerging diabetic wound healing agent in the industry of nanomedicines.

[20] *Luchsinger JA, Younes N, Manly JJ et al.* **Association of Glycemia, Lipids, and Blood Pressure With Cognitive Performance in People With Type 2 Diabetes in the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study**. Diabetes Care 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34285097
ABSTRACT
OBJECTIVE: Type 2 diabetes is a risk factor for cognitive impairment. We examined the relation of glycemia, lipids, blood pressure (BP), hypertension history, and statin use with cognition in the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE). RESEARCH DESIGN AND METHODS: Cross-sectional analyses from GRADE at baseline examined the association of glycemia (hemoglobin A(1c) [HbA(1c)]), LDL, systolic BP (SBP) and diastolic BP (DBP), hypertension history, and statin use with cognition assessed by the Spanish English Verbal Learning Test, letter and animal fluency tests, and Digit Symbol Substitution Test (DSST). RESULTS: Among 5,047 GRADE participants, 5,018 (99.4%) completed cognitive assessments. Their mean age was 56.7 ± 10.0 years, and 36.4% were women. Mean diabetes duration was 4.0 ± 2.7 years. HbA(1c) was not related to cognition. Higher LDL was related to modestly worse DSST scores, whereas statin use was related to modestly better DSST scores. SBP between 120 and 139 mmHg and DBP between 80 and 89 mmHg were related to modestly better DSST scores. Hypertension history was not related to cognition. CONCLUSIONS: In people with type 2 diabetes of a mean duration of <5 years, lower LDL and statin use were related to modestly better executive cognitive function. SBP levels in the range of 120-139 mmHg and DBP levels in the range of 80-89 mmHg, but not lower levels, were related to modestly better executive function. These differences may not be clinically significant.

[21] *Hero C, Karlsson SA, Franzén S et al.* **Impact of Socioeconomic Factors and Gender on Refill Adherence and Persistence to Lipid-Lowering Therapy in Type 1 Diabetes**. Diabetes Ther 2021; 12:2371-2386.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34292559
ABSTRACT
INTRODUCTION: Lipid-lowering therapy (LLT) reduces the risk of cardiovascular disease (CVD) in patients with type 1 diabetes (T1D). However, socioeconomic factors and gender may have an impact on the adherence to and non-persistence with LLT. METHODS: This was a nationwide register-based cohort study that included 6192 individuals with T1D aged ≥ 18 years who were registered in the Swedish National Diabetes Register and had initiated novel use of LLT. Information on socioeconomic parameters (source: Statistics Sweden) and comorbidity (source: National Patient Register) was collected. The individuals were followed for 36 months, and adherence to LLT was analyzed according to age, socioeconomics and gender. The medication possession ratio (MPR; categorized into ≤ 80% and > 80%) and non-persistence (discontinuation) with medication was calculated after 18 and 36 months. RESULTS: Individuals older than 53 years were more adherent to LLT (MPR>80%) than those younger than 36 years (odds ratio [(OR] 1.30, p<0.0001) at 36 months. Women were more adherent and less prone to discontinue LLT at 18 months (OR 1.05, p=0.0005 and OR 0.95, p=0.0004, respectively), but not at 36 months. Divorced individuals were less adherent than married ones (OR 0.93, p=0.0005) and discontinued LLT more often than the latter (OR 1.06, p=0.003). Education had no impact on adherence, but individuals with higher incomes discontinued LLT less frequently than those with lower incomes. Individuals with a country of origin other than Sweden discontinued LLT more often. CONCLUSION: Lower adherence to LLT in individuals with T1D was associated with male gender, younger age, marital status and country of birth. These factors should be considered when evaluating adherence to LLT in clinical practice, with the aim to help patients achieve full cardioprotective treatment.

[22] *Bułdak Ł*. **The treatment of heterozygous familial hypercholesterolemia - a local perspective**. Endokrynol Pol 2021; 72:189-190.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34292576
ABSTRACT
none.

[23] *Dai L, Zuo Y, You Q et al.* **Efficacy and safety of bempedoic acid in patients with hypercholesterolemia: A systematic review and meta-analysis of randomized controlled trials**. European journal of preventive cardiology 2021; 28:825-833.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34298558
ABSTRACT
AIM: Bempedoic acid is a novel oral drug, which has been increasingly researched to play an important role in the treatment of hypercholesterolemia recently. However, results from original studies were inconsistent and inconclusive. We aimed to conduct a meta-analysis to quantitatively appraise the efficacy and safety of bempedoic acid. METHODS: PubMed, Embase, Web of Science and Scopus were searched from inception to 30 January 2020. We included randomized controlled trials that compared the efficacy and safety of bempedoic acid with placebo in patients with hypercholesterolemia. Results from trials were presented as mean differences or odds ratios (ORs)

with 95% confidence intervals (CIs) and were pooled by random or fixed effects model. The risk of bias and heterogeneity among trials were also assessed and analyzed. RESULTS: Pooled analysis of 10 eligible trials showed that bempedoic acid treatment resulted in greater lowering of the low-density lipoprotein cholesterol level than the placebo group (mean difference -23.16%, 95% CI -26.92% to -19.04%). We also found that improvements in lipid parameters and biomarkers were still maintained at weeks 24 and 52 from the long-term trials. As for safety, bempedoic acid did not increase the risk of overall adverse events (OR 1.02, 95% CI 0.88 to 1.18). However, the incidence of adverse events leading to discontinuation was higher in the bempedoic acid group (OR 1.44, 95% CI 1.14 to 1.82). CONCLUSIONS: Available evidence from randomized controlled trials suggests that bempedoic acid provides a well-tolerated and effective therapeutic option for lipid lowering in patients with hyperlipidemia.

[24] *Genser B, Wanner C, März W*. **A scoring system for predicting individual treatment effects of statins in type 2 diabetes patients on haemodialysis**. European journal of preventive cardiology 2021; 28:838-851.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34298559
ABSTRACT
AIMS: Haemodialysis patients have high cardiovascular disease risk. Although statins reduce this risk in chronic kidney disease, randomised trials in haemodialysis patients show no benefit. Post-hoc analyses of the German Diabetes Dialysis (4D) study identified patient-specific markers associated with heterogeneous treatment effects. We combined these markers to develop a score for predicting individual effects of statins in these patients. METHODS AND RESULTS: We used data from the 4D study, enrolling 1255 haemodialysis patients with type 2 diabetes mellitus, randomised to atorvastatin or placebo and followed for a composite cardiovascular endpoint. We calculated two scores: score 1 based on all 23 predictive markers and score 2 based on 17 clinically accessible markers. Groups stratified by score 1 showed differential treatment effects: for score <26 (458 patients; 36%), the hazard ratio (95% confidence interval) was 1.54 (1.16-2.03), suggesting harm; for 26-31 (331 patients; 26%), it was 1.03 (0.72-1.48), suggesting a neutral effect; and for >31 (466 patients; 38%), it was 0.43 (0.30-0.60), suggesting a benefit. Statins also significantly reduced all-cause mortality in the benefit group. Stratification by score 2 yielded similar results but a smaller group gaining benefit (360 patients). CONCLUSION: Statin effects in haemodialysis patients can be predicted by markers associated with plausible relevant mechanisms including cholesterol metabolism, atherosclerosis, protein energy wasting, or competing risks. In clinical practice, the score could aid in risk stratification, not only to select patients who benefit from statins but also to identify those whom treatment could harm.

[25] *Harris DE, Lacey A, Akbari A et al.* **Achievement of European guideline-recommended lipid levels post-percutaneous coronary intervention: A population-level observational cohort study**. European journal of preventive cardiology 2021; 28:854-861.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34298561
ABSTRACT
AIMS: European Society of Cardiology/European Atherosclerosis Society 2019 guidelines recommend more aggressive lipid targets in high- and very high-risk patients and the addition of adjuvant treatments to statins in uncontrolled patients. We aimed to assess (a) achievement of prior

and new European Society of Cardiology/European Atherosclerosis Society lipid targets and (b) lipid-lowering therapy prescribing in a nationwide cohort of very high-risk patients. METHODS: We conducted a retrospective observational population study using linked health data in patients undergoing percutaneous coronary intervention (2012-2017). Follow-up was for one-year post-discharge. RESULTS: Altogether, 10,071 patients had a documented LDL-C level, of whom 48% had low-density lipoprotein cholesterol (LDL-C)<1.8 mmol/l (2016 target) and (23%) <1.4 mmol/l (2019 target). Five thousand three hundred and forty patients had non-high-density lipoprotein cholesterol (non-HDL-C) documented with 57% <2.6 mmol/l (2016) and 37% <2.2 mmol/l (2019). In patients with recurrent vascular events, fewer than 6% of the patients achieved the 2019 LDL-C target of <1.0 mmol/l. A total of 10,592 patients had triglyceride (TG) levels documented, of whom 14% were ≥2.3 mmol/l and 41% ≥1.5 mmol/l (2019). High-intensity statins were prescribed in 56.4% of the cohort, only 3% were prescribed ezetimibe, fibrates or prescription-grade N-3 fatty acids. Prescribing of these agents was lower amongst patients above target LDL-C, non-HDL-C and triglyceride levels. Females were more likely to have LDL-C, non-HDL-C and triglyceride levels above target. CONCLUSION: There was a low rate of achievement of the new European Society of Cardiology/European Atherosclerosis Society lipid targets in this large post-percutaneous coronary intervention population and relatively low rates of intensive lipid-lowering therapy prescribing in those with uncontrolled lipids. There is considerable potential to optimise lipid-lowering therapy further through statin intensification and appropriate use of novel lipid-lowering therapy, especially in women.

[26] *Ichikawa K, Miyoshi T, Osawa K et al.* **Incremental prognostic value of non-alcoholic fatty liver disease over coronary computed tomography angiography findings in patients with suspected coronary artery disease**. European journal of preventive cardiology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34279027

ABSTRACT

AIMS: This study aimed to investigate additional risk stratification benefits of hepatic steatosis (HS) concurrently assessed during coronary computed tomography angiography (CTA) in a large patient cohort with suspected stable coronary artery disease (CAD). METHODS AND RESULTS: In this prospective study, 1148 Japanese outpatients without a history of CAD who underwent coronary CTA for suspected stable CAD (mean age 64 ± 14 years) were included. HS, defined on CT as a hepatic-to-spleen attenuation ratio of <1.0, was examined just before the evaluation of adverse CTA findings, defined as obstructive and/or high-risk plaque. The major adverse cardiac events (MACE) were the composite of cardiac death, acute coronary syndrome, and late revascularization. The incremental predictive value of HS was evaluated using the global $\chi 2$ test and C-statistic. HS was identified in 247 (22%) patients. During a median follow-up of 3.9 years, MACE was observed in 40 (3.5%) patients. HS was significantly associated with MACE in a model that included adverse CTA findings (hazard ratio 4.01, 95% confidence interval 2.12-7.59, $P < 0.001$). By adding HS to the Framingham risk score and adverse CTA findings, the global $\chi 2$ score and C-statistic significantly increased from 29.0 to 49.5 ($P < 0.001$) and 0.74 to 0.81 ($P = 0.026$), respectively. In subgroup analyses in patients with diabetes mellitus and metabolic syndrome, HS had significant additive predictive value for MACE over the Framingham risk score and adverse CTA findings. CONCLUSION: In patients with suspected stable CAD, concurrent evaluation of HS during coronary CTA enables more accurate detection of patients at higher risk of MACE.

[27] *Mahmood T, Minnier J, Ito MK et al.* **Discordant responses of plasma low-density lipoprotein cholesterol and lipoprotein(a) to alirocumab: A pooled analysis from 10 ODYSSEY Phase 3 studies**. European journal of preventive cardiology 2021; 28:816-822.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34298554
ABSTRACT
AIMS: Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors consistently reduce low-density lipoprotein cholesterol (LDL-C) by 50-60% and lipoprotein(a) (Lp(a)) by 20-30%, but the mechanism of Lp(a) lowering remains unclear. If Lp(a) is cleared by the LDL receptor, similar to LDL-C, then one would expect PCSK9 inhibition to induce a concordant LDL-C/Lp(a) response in an approximately 2:1 ratio. We aim to determine the prevalence of discordant plasma LDL-C/Lp(a) response to the PCSK9 inhibitor alirocumab. METHODS: This is a post hoc, pooled analysis of 10 randomized controlled trials from the ODYSSEY Phase 3 clinical trial program for alirocumab. Patients enrolled in the trials were high cardiovascular risk and/or with heterozygous familial hypercholesterolemia. The primary end point was prevalence of discordant LDL-C/Lp(a) response to alirocumab at 24 weeks. Discordant response was defined as LDL-C reduction >35% and Lp(a) reduction ≤10%, or LDL-C reduction ≤35% and Lp(a) reduction >10%. RESULTS: Of the 1709 patients in the pooled study cohort, 62.4% were male, and the mean age was 59.2 (SD: 11.0) years. Baseline mean LDL-C was 126.5 (SD: 46.3) mg/dL and baseline median Lp(a) was 46.9 (interquartile range: 21.8-89.0) mg/dL. Total prevalence of discordant LDL-C/Lp(a) response was 21.5% (12.6% with LDL-C >35% reduction and Lp(a) ≤10% reduction; 8.9% with LDL-C ≤35% reduction and Lp(a) >10% reduction). Baseline Lp(a) and familial hypercholesterolemia status did not affect discordance. CONCLUSION: A high prevalence of discordant LDL-C/Lp(a) response was observed with alirocumab, further suggesting that PCSK9 inhibitor therapy with alirocumab reduces plasma Lp(a) through alternative pathways to LDL receptor clearance.

[28] *Reeskamp LF, Tromp TR, Defesche JC et al.* **Next-generation sequencing to confirm clinical familial hypercholesterolemia**. European journal of preventive cardiology 2021; 28:875-883.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34298557
ABSTRACT
BACKGROUND: Familial hypercholesterolemia is characterised by high low-density lipoprotein-cholesterol levels and is caused by a pathogenic variant in LDLR, APOB or PCSK9. We investigated which proportion of suspected familial hypercholesterolemia patients was genetically confirmed, and whether this has changed over the past 20 years in The Netherlands. METHODS: Targeted next-generation sequencing of 27 genes involved in lipid metabolism was performed in patients with low-density lipoprotein-cholesterol levels greater than 5 mmol/L who were referred to our centre between May 2016 and July 2018. The proportion of patients carrying likely pathogenic or pathogenic variants in LDLR, APOB or PCSK9, or the minor familial hypercholesterolemia genes LDLRAP1, ABCG5, ABCG8, LIPA and APOE were investigated. This was compared with the yield of Sanger sequencing between 1999 and 2016. RESULTS: A total of 227 out of the 1528 referred patients (14.9%) were heterozygous carriers of a pathogenic variant in LDLR (80.2%), APOB (14.5%) or PCSK9 (5.3%). More than 50% of patients with a Dutch Lipid Clinic Network score of 'probable' or 'definite' familial hypercholesterolemia were familial hypercholesterolemia mutation-positive; 4.8% of the familial hypercholesterolemia mutation-negative patients carried a variant in one of the minor familial hypercholesterolemia genes. The mutation detection rate has decreased over the past two decades,

especially in younger patients in which it dropped from 45% in 1999 to 30% in 2018. CONCLUSIONS: A rare pathogenic variant in LDLR, APOB or PCSK9 was identified in 14.9% of suspected familial hypercholesterolemia patients and this rate has decreased in the past two decades. Stringent use of clinical criteria algorithms is warranted to increase this yield. Variants in the minor familial hypercholesterolemia genes provide a possible explanation for the familial hypercholesterolemia phenotype in a minority of patients.

[29] *Sever P, Gouni-Berthold I, Keech A et al.* **LDL-cholesterol lowering with evolocumab, and outcomes according to age and sex in patients in the FOURIER Trial**. European journal of preventive cardiology 2021; 28:805-812.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34298555

ABSTRACT

AIMS: Some trials have reported diminished efficacy for statins in the elderly, and in women compared with men. We examined the efficacy and safety of evolocumab by patient age and sex in the FOURIER trial, the first major cardiovascular outcome trial of a PCSK9 inhibitor. METHODS AND RESULTS: FOURIER was a randomised, double blind trial, comparing evolocumab with placebo in 27,564 patients with atherosclerotic cardiovascular disease receiving statin therapy (median follow-up 2.2 years). The primary endpoint was cardiovascular death, myocardial infarction, stroke, hospitalisation for unstable angina or coronary revascularisation. Cox proportional hazards models were used to assess the efficacy of evolocumab versus placebo stratified by quartiles of patient age and by sex. There were small variations in the cardiovascular event rate across the age range (for the primary endpoint, Kaplan-Meier at 3 years 15.6%, >69 years, vs. 15.1%, ≤56 years, P = 0.45); however, the relative efficacy of evolocumab was consistent regardless of patient age (for the primary endpoint (Q1 hazard ratio, 95% confidence interval) 0.83, 0.72-0.96, Q2 0.88, 0.76-1.01, Q3 0.82, 0.71-0.95, Q4 0.86, 0.74-1.00; Pinteraction = 0.91), and the key secondary endpoint (cardiovascular death, myocardial infarction, stroke) (Q1 0.74 (0.61-0.89), Q2 0.83 (0.69-1.00), Q3 0.78 (0.65-0.94), Q4 0.82 (0.69-0.98)); Pinteraction = 0.81). Women had a lower primary endpoint rate than men (Kaplan-Meier at 3 years 12.5 vs. 15.3%, respectively, P < 0.001). Relative risk reductions in the primary endpoint and key secondary endpoint were similar in women (0.81 (0.69-0.95) and 0.74 (0.61-0.90), respectively) compared with men (0.86 (0.80-0.94) and 0.81 (0.73-0.90), respectively), Pinteraction = 0.48 and 0.44, respectively. Adverse events were more common in women and with increasing age but, with the exception of injection site reactions, there were no important significant differences reported by those assigned evolocumab versus placebo. CONCLUSIONS: The efficacy and safety of evolocumab are similar throughout a broad range of ages and in both men and women.

[30] *Cai Y, Liu X, Zhang L et al.* **Prevalence and characteristics of atherosclerotic plaque: Left compared with right arteries and anterior compared with posterior circulation stroke**. European journal of radiology 2021; 142:109862.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34298390

ABSTRACT

PURPOSE: To evaluate atherosclerotic plaque prevalence and characteristics between left and right cervicocephalic arteries and between anterior and posterior circulation stroke (ACS and PCS). METHODS: This retrospective study included 284 patients with acute ischemic stroke (199 ACS and 85 PCS) involving large-artery atherosclerosis or small-artery occlusion. We assessed atherosclerotic

plaque prevalence and characteristics (plaque type, plaque surface morphology, plaque distribution, location of calcified nodules and plaque thickness) in each segment and their comparisons between left and right arteries and between ACS and PCS. RESULTS: The left subclavian artery (L-SA), common carotid artery (L-CCA) and intracranial vertebral artery (L-IVA) had significantly higher prevalence of atherosclerotic plaque than the right (R) corresponding arteries (70.1% versus 59.5%, P = 0.008), (48.1% versus 28.9%, P < 0.001), (23.9% versus 16%, P = 0.018), respectively. L-SA had a higher prevalence of mixed plaque (non-calcified > calcified) (19.6% versus 16.4%) and noncalcified plaque (51.9% versus 31.7%), and a lower prevalence of calcified plaque (8.9% versus 23.3%) and mixed plaque (calcified > non-calcified) (19.6% versus 28.6%) than R-SA, P < 0.001. The distribution of plaque type in the SA and extracranial vertebral artery (EVA) were significantly different between ACS and PCS. The soft plaque thickness of SA in PCS was significantly greater than that in ACS (3.85 ± 1.27 versus 3.51 ± 1.04, P = 0.032). CONCLUSIONS: Atherosclerotic plaque prevalence and characteristics vary in different segments, sides and between ACS and PCS. These differences should be noted during plaque diagnosis.

[31] *Wang X, Song J, He Q, You C*. **Pharmacological Treatment in the Management of Chronic Subdural Hematoma**. Frontiers in aging neuroscience 2021; 13:684501.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34276343

ABSTRACT

Background: Several pharmacological treatments have been used to treat patients with chronic subdural hematoma (CSDH), although little is known about the comparative effectiveness of different classes of medication. We performed a Bayesian network meta-analysis to compare and rank the efficacy and safety of five drug regimens to determine the best treatment for this group of patients. Methods: We systematically searched PubMed, Medline, clinicaltrials.gov, the Cochrane database, and Embase to identify relevant randomized clinical trials (RCTs) comparing drug treatments in adult patients with CSDH. A network meta-analysis was conducted using a Bayesian framework. Random- and fixed-effects models were used to pool the network results, and the preferred model was selected by comparing the deviance information criteria (DIC). Efficacy outcomes included recurrence requiring surgery, changes in hematoma volume, and a good recovery. The safety outcomes were treatment-related adverse events and all-cause mortality. Results: In this Bayesian network meta-analysis, available data were obtained from 12 eligible trials, including 2,098 patients and 5 techniques. Compared to placebo, atorvastatin (RR: 0.45, 95% CrI: 0.24-0.81) and dexamethasone (RR: 0.38, 95% CrI: 0.22-0.63) were similarly effective in reducing recurrence requiring surgery by 55% and 62%, respectively. Dexamethasone (RR: 0.46, 95% CrI: 0.23-0.91) was more effective in reducing recurrence requiring surgery than goreisan. Additionally, atorvastatin reduced the hematoma volume to a greater extent than placebo (MD: -7.44, 95% CrI: -9.49 to -5.43) or goreisan (MD: -14.09, 95% CrI: -23.35 to -4.82). Moreover, tranexamic acid (MD: -12.07, 95% CrI: -21.68 to -2.29) reduced the hematoma volume to a greater extent than goreisan. No significant differences were detected between drugs and placebo with regard to a good recovery. In terms of safety, dexamethasone (RR: 1.96, 95% CrI: 1.20-3.28) increased the risk of mortality compared to placebo. Conclusion: These findings suggest that dexamethasone is the best treatment to reduce recurrence and atorvastatin is the best treatment to reduce hematoma volume in patients with CSDH. However, clinicians should pay close attention to the elevated risk of all-cause mortality and potential adverse events caused by

dexamethasone. Future well-designed RCTs with more participants are needed to verify these findings. Clinical Trial Registration: http://osf.io/u9hqp.

[32] *Abu-Much A, Nof E, Bragazzi NL et al.* **Ethnic Disparity in Mortality Among Ischemic Heart Disease Patients. A-20 Years Outcome Study From Israel**. Frontiers in cardiovascular medicine 2021; 8:661390.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34277726
ABSTRACT
Background: Long-term morbidity and mortality data among ischemic heart disease (IHD) patients of different ethnicities are conflicting. We sought to determine the independent association of ethnicity and all-cause mortality over two decades of follow-up of Israeli patients. Methods: Our study comprised 15,524 patients including 958 (6%) Arab patients who had been previously enrolled in the Bezafibrate Infarction Prevention (BIP) registry between February 1, 1990, and October 31, 1992, and subsequently followed-up for long-term mortality. We compared clinical characteristics and outcomes of Israeli Arabs and Jews. Propensity score matching (PSM) (1:2 ratios) was used for validation. Results: Arab patients were significantly younger (56 ± 7 years vs. 60 ± 7 years; $p < 0.001$; respectively), and had more cardiovascular disease (CVD) risk factors. Kaplan-Meier survival analysis showed that all-cause mortality was significantly higher among Arab patients (67 vs. 61%; log-rank $p < 0.001$). Multivariate adjusted analysis showed that mortality risk was 49% greater (HR 1.49; 95% CI: 1.37-1.62; $p < 0.001$) among Arabs. Conclusions: Arab ethnicity is independently associated with an increased 20-year all-cause mortality among patients with established IHD.

[33] *Guo B, Li Z, Tu P et al.* **Molecular Imaging and Non-molecular Imaging of Atherosclerotic Plaque Thrombosis**. Frontiers in cardiovascular medicine 2021; 8:692915.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34291095
ABSTRACT
Thrombosis in the context of atherosclerosis typically results in life-threatening consequences, including acute coronary events and ischemic stroke. As such, early detection and treatment of thrombosis in atherosclerosis patients is essential. Clinical diagnosis of thrombosis in these patients is typically based upon a combination of imaging approaches. However, conventional imaging modalities primarily focus on assessing the anatomical structure and physiological function, severely constraining their ability to detect early thrombus formation or the processes underlying such pathology. Recently, however, novel molecular and non-molecular imaging strategies have been developed to assess thrombus composition and activity at the molecular and cellular levels more accurately. These approaches have been successfully used to markedly reduce rates of atherothrombotic events in patients suffering from acute coronary syndrome (ACS) by facilitating simultaneous diagnosis and personalized treatment of thrombosis. Moreover, these modalities allow monitoring of plaque condition for preventing plaque rupture and associated adverse cardiovascular events in such patients. Sustained developments in molecular and non-molecular imaging technologies have enabled the increasingly specific and sensitive diagnosis of atherothrombosis in animal studies and clinical settings, making these technologies invaluable to patients' health in the future. In the present review, we discuss current progress regarding the non-molecular and molecular imaging of thrombosis in different animal studies and atherosclerotic patients.

[34] *Zuo W, Sun R, Zhang X et al.* **The Association Between Quantitative Flow Ratio and Intravascular Imaging-defined Vulnerable Plaque Characteristics in Patients With Stable Angina and Non-ST-segment Elevation Acute Coronary Syndrome**. Frontiers in cardiovascular medicine 2021; 8:690262.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34277736

ABSTRACT

Background: This study aimed to examine whether quantitative flow ratio (QFR), an angiography-based computation of fractional flow reserve, was associated with intravascular imaging-defined vulnerable plaque features, such as thin cap fibroatheroma (TCFA) in patients with stable angina, and non-ST-segment elevation acute coronary syndrome. Methods: Patients undergoing optical coherence tomography (OCT) or intravascular ultrasound (IVUS) examinations were identified from two prospective studies and their interrogated vessels were assessed with QFR. Lesions in the OCT cohort were classified into tertiles: QFR-T1 (QFR ≤ 0.85), QFR-T2 (0.85 < QFR ≤ 0.93), and QFR-T3 (QFR > 0.93). Lesions in the IVUS cohort were classified dichotomously as low or high QFR groups. Results: This post-hoc analysis included 132 lesions (83 for OCT and 49 for IVUS) from 126 patients. The prevalence of OCT-TCFA was significantly higher in QFR-T1 (50%) than in QFR-T2 (14%) and QFR-T3 (19%) (p = 0.003 and 0.018, respectively). Overall significant differences were also observed among tertiles in maximum lipid arc, thinnest fibrous cap thickness, and minimal lumen area (p = 0.017, 0.040, and <0.001, respectively). Thrombus was more prevalent in QFR-T1 (39%) than in QFR-T2 (3%), and QFR-T3 (12%) (p = 0.001 and 0.020, respectively). In the multivariable analysis, QFR ≤ 0.80 remained as a significant determinant of OCT-TCFA regardless of the presence of NSTE-ACS and the level of low-density lipoprotein cholesterol (adjusted OR: 4.387, 95% CI 1.297-14.839, p = 0.017). The diagnostic accuracy of QFR was moderate in identifying lesions with OCT-TCFA (area under the curve: 0.72, 95% CI 0.58-0.86, p = 0.003). In the IVUS cohort, significant differences were found between two groups in minimal lumen area and plaque burden but not in the distribution of virtual histology (VH)-TCFA (p = 0.025, 0.036, and 1.000, respectively). Conclusions: Lower QFR was related to OCT-defined plaque vulnerability in angiographically mild-to-intermediate lesions. The QFR might be a useful tool for ruling out high-risk plaques without using any pressure wire or vasodilator.

[35] *Xing L, Peng F, Liang Q et al.* **Clinical Characteristics and Risk of Diabetic Complications in Data-Driven Clusters Among Type 2 Diabetes**. Frontiers in endocrinology 2021; 12:617628.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34276555

ABSTRACT

BACKGROUND: This study aimed to cluster newly diagnosed patients and patients with long-term diabetes and to explore the clinical characteristics, risk of diabetes complications, and medication treatment related to each cluster. RESEARCH DESIGN AND METHODS: K-means clustering analysis was performed on 1,060 Chinese patients with type 2 diabetes based on five variables (HbA1c, age at diagnosis, BMI, HOMA2-IR, and HOMA2-B). The clinical features, risk of diabetic complications, and the utilization of elven types of medications agents related to each cluster were evaluated with the chi-square test and the Tukey-Kramer method. RESULTS: Four replicable clusters were identified, severe insulin-resistant diabetes (SIRD), severe insulin-deficient diabetes (SIDD), mild obesity-related diabetes (MOD), and mild age-related diabetes (MARD). In terms of clinical characteristics, there were significant differences in blood pressure, renal function, and lipids among

clusters. Furthermore, individuals in SIRD had the highest prevalence of stages 2 and 3 chronic kidney disease (CKD) (57%) and diabetic peripheral neuropathy (DPN) (67%), while individuals in SIDD had the highest risk of diabetic retinopathy (32%), albuminuria (31%) and lower extremity arterial disease (LEAD) (13%). Additionally, the difference in medication treatment of clusters were observed in metformin (p = 0.012), α-glucosidase inhibitor (AGI) (p = 0.006), dipeptidyl peptidase 4 inhibitor (DPP-4) (p = 0.017), glucagon-like peptide-1 (GLP-1) (p <0.001), insulin (p <0.001), and statins (p = 0.006). CONCLUSIONS: The newly diagnosed patients and patients with long-term diabetes can be consistently clustered into featured clusters. Each cluster had significantly different patient characteristics, risk of diabetic complications, and medication treatment.

[36] *Kim HS, Lee H, Providо SMP et al.* **Association Between Diet Quality and Prevalence of Obesity, Dyslipidemia, and Insulin Resistance Among Filipino Immigrant Women in Korea: The Filipino Women's Diet and Health Study**. Frontiers in public health 2021; 9:647661.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34277535

ABSTRACT

Objectives: Diet quality may be a key modifiable factor for the prevention of non-communicable disease. We aimed to investigate the association between diet quality and prevalence of obesity, dyslipidemia, and insulin resistance among Filipino immigrant women in Korea. Methods: A total of 413 participants from the 2014-2016 baseline population of the Filipino Women's Diet and Health Study (FiLWHEL) were examined. Individual dietary intakes were evaluated through 24-h recalls and then converted into two dietary quality assessments: Minimum Dietary Diversity for Women (MDD-W) developed by the Food and Agriculture Organization (FAO) and the Data Derived Inflammation Index (DDII) originally developed by our group. Fasting blood levels of triglycerides, high-density lipoprotein cholesterols, glucose, and insulin were measured. We used logistic regression models for odds ratios (ORs) with 95% confidence intervals (CIs). Results: We found a statistically significant association between MDD-W scores and decreased prevalence of abdominal obesity; ORs (95% CIs) of the 3rd vs. 1st tertiles were 0.58 (0.36-0.94; p for trend = 0.029). Increased DDII was associated with elevated prevalence of dyslipidemia and insulin resistance; ORs (95% CIs) of the 5th vs. 1-3rd quintiles were 6.44 (2.56-16.20) for triglycerides (TG), 3.90 (1.92-7.90) for low-density lipoprotein (LDL) cholesterol, 3.36 (1.81-6.24) for total cholesterol (TC), 6.25 (2.53-15.41) for abnormal TG/HDL ratios, 3.59 (1.96-6.59) for HbA1c, 2.61 (1.11-6.17) for fasting blood glucose levels, 9.67 (4.16-22.48) for insulin levels, and 9.73 (4.46-21.25) for homeostasis model assessment of insulin resistance (HOMA-IR) (p for trend <0.001 for all, except 0.033 for fasting blood glucose). Conclusions: Greater dietary diversity was inversely associated with the prevalence of abdominal obesity in Filipino immigrant women. Proinflammatory scores based on diet and lifestyle factors were associated with an increased prevalence of dyslipidemia and insulin resistance. Further, epidemiological studies on the relationship between dietary acculturation and chronic disease are warranted.

[37] *Fukase T, Dohi T, Kato Y et al.* **High Apolipoprotein E Levels Predict Adverse Limb Events in Patients with Peripheral Artery Disease Due to Peripheral Artery Disease Undergoing Endovascular Treatment and On-Statin Treatment**. Int Heart J 2021; 62:872-878.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34276016

ABSTRACT

Little is known about the association between limb prognosis in peripheral artery disease and apolipoprotein E (apoE). We evaluated the long-term impact of apoE on adverse limb events in patients with intermittent claudication receiving statin treatment.A total of 218 consecutive patients (mean age, 73 ± 8 years; 81% men) with intermittent claudication who underwent their first intervention between 2009 and 2020 were included in this study. All patients had achieved LDL-C < 100 mg/dL on statin treatment and were divided into two groups based on the apoE value (≥ 4.7 or < 4.7 mg/dL). We evaluated the incidence of major adverse limb events (MALEs), including vessel revascularization and limb ischemia development.A total of 39 and 179 patients were allocated to the higher and lower apoE groups, respectively. Compared to the lower apoE group, the higher apoE group had a significantly higher total cholesterol level, triglyceride level, and non-high-density lipoprotein cholesterol level. During the median follow-up period of 3.6 years, 30 patients (13.8%) developed MALEs. Kaplan-Meier analysis revealed that the cumulative incidence of MALEs in the higher apoE group was significantly higher than that in the lower apoE group (44.0% versus 21.6%, log-rank test, P = 0.002). During multivariable Cox hazard analysis, higher apoE level (≥ 4.7 mg/dL) (hazard ratio, 2.61; 95% confidence interval, 1.18-5.70, P = 0.019) was the only strong independent predictor of MALEs.ApoE levels could be a strong predictor and residual risk for long-term limb prognosis in patients with intermittent claudication and achieving LDL-C < 100 mg/dL with statin treatment.

[38] *Perez-Lasierra JL, Casajús JA, Casasnovas JA et al.* **Can Physical Activity Reduce the Risk of Cognitive Decline in Apolipoprotein e4 Carriers? A Systematic Review**. International journal of environmental research and public health 2021; 18.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34299687
ABSTRACT
Physical activity (PA) reduces the risk of cognitive decline (CD) in the general population. However, little is known about whether the presence of the apolipoprotein E epsilon 4 allele (APOE e4) could modify this beneficial effect. The aim of this systematic review was to analyze and synthetize the scientific evidence related to PA levels and CD risk in cognitively healthy APOE e4 carriers. Four electronic databases were analyzed. Only original articles with longitudinal study design were selected to analyze the relationship between PA and CD in APOE e4 carriers. Five studies were included in the systematic review. All studies except one stated that PA is a protective factor against CD in APOE e4 carriers. Moreover, partial support was found for the hypothesis that a greater amount and intensity of PA are more beneficial in CD prevention. The results support the idea that PA is a protective factor against CD in APOE e4 carriers. Nevertheless, it would be necessary to carry out further studies that would allow these findings to be contrasted.

[39] *Cammisotto V, Baratta F, Castellani V et al.* **Proprotein Convertase Subtilisin Kexin Type 9 Inhibitors Reduce Platelet Activation Modulating ox-LDL Pathways**. International journal of molecular sciences 2021; 22.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34281247
ABSTRACT
Background: Proprotein convertase subtilisin kexin type 9 inhibitors (PCSK9i) lower LDL-cholesterol and slow atherosclerosis preventing cardiovascular events. While it is known that circulating PCSK9 enhances platelet activation (PA) and that PCSK9i reduce it, the underlying mechanism is not still

clarified. Methods: In a multicenter before-after study in 80 heterozygous familial hypercholesterolemia (HeFH) patients on treatment with maximum tolerated statin dose ± ezetimibe, PA, soluble-NOX2-derived peptide (sNOX2-dp), and oxidized-LDL (ox-LDL) were measured before and after six months of PCSK9i treatment. In vitro study investigates the effects of plasma from HeFH patients before and after PCK9i on PA in washed platelets (wPLTs) from healthy subjects. Results: Compared to baseline, PCSK9i reduced the serum levels of LDL-c, ox-LDL, Thromboxane (Tx) B2, sNOX2-dp, and PCSK9 ($p < 0.001$). The decrease of TxB2 correlates with that of ox-LDL, while ox-LDL reduction correlated with PCSK9 and sNOX2-dp delta. In vitro study demonstrated that wPLTs resuspended in plasma from HeFH after PCSK9i treatment induced lower PA and sNOX2-dp release than those obtained using plasma before PCSK9i treatment. This reduction was vanished by adding ox-LDL. ox-LDL-induced PA was blunted by CD36, LOX1, and NOX2 inhibition. Conclusions: PCSK9i treatment reduces PA modulating NOX2 activity and in turn ox-LDL formation in HeFH patients.

[40] *Chen PY, Gao WY, Liou JW et al.* **Angiopoietin-Like Protein 3 (ANGPTL3) Modulates Lipoprotein Metabolism and Dyslipidemia**. International journal of molecular sciences 2021; 22.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34298929

ABSTRACT

Dyslipidemia is characterized by increasing plasma levels of low-density lipoprotein-cholesterol (LDL-C), triglycerides (TGs) and TG-rich lipoproteins (TGRLs) and is a major risk factor for the development of atherosclerotic cardiovascular disorders (ASCVDs). It is important to understand the metabolic mechanisms underlying dyslipidemia to develop effective strategies against ASCVDs. Angiopoietin-like 3 (ANGPTL3), a member of the angiopoietin-like protein family exclusively synthesized in the liver, has been demonstrated to be a critical regulator of lipoprotein metabolism to inhibit lipoprotein lipase (LPL) activity. Genetic, biochemical, and clinical studies in animals and humans have shown that loss of function, inactivation, or downregulated expression of ANGPTL3 is associated with an obvious reduction in plasma levels of TGs, LDL-C, and high-density lipoprotein-cholesterol (HDL-C), atherosclerotic lesions, and the risk of cardiovascular events. Therefore, ANGPTL3 is considered an alternative target for lipid-lowering therapy. Emerging studies have focused on ANGPTL3 inhibition via antisense oligonucleotides (ASOs) and monoclonal antibody-based therapies, which have been carried out in mouse or monkey models and in human clinical studies for the management of dyslipidemia and ASCVDs. This review will summarize the current literature on the important role of ANGPTL3 in controlling lipoprotein metabolism and dyslipidemia, with an emphasis on anti-ANGPTL3 therapies as a potential strategy for the treatment of dyslipidemia and ASCVDs.

[41] *Gaillard D, Masson D, Garo E et al.* **Muricholic Acids Promote Resistance to Hypercholesterolemia in Cholesterol-Fed Mice**. International journal of molecular sciences 2021; 22.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34281217

ABSTRACT

BACKGROUND AND AIMS: Hypercholesterolemia is a major risk factor for atherosclerosis and cardiovascular diseases. Although resistant to hypercholesterolemia, the mouse is a prominent model in cardiovascular research. To assess the contribution of bile acids to this protective phenotype, we explored the impact of a 2-week-long dietary cholesterol overload on cholesterol and bile acid

metabolism in mice. METHODS: Bile acid, oxysterol, and cholesterol metabolism and transport were assessed by quantitative real-time PCR, western blotting, GC-MS/MS, or enzymatic assays in the liver, the gut, the kidney, as well as in the feces, the blood, and the urine. RESULTS: Plasma triglycerides and cholesterol levels were unchanged in mice fed a cholesterol-rich diet that contained 100-fold more cholesterol than the standard diet. In the liver, oxysterol-mediated LXR activation stimulated the synthesis of bile acids and in particular increased the levels of hydrophilic muricholic acids, which in turn reduced FXR signaling, as assessed in vivo with Fxr reporter mice. Consequently, biliary and basolateral excretions of bile acids and cholesterol were increased, whereas portal uptake was reduced. Furthermore, we observed a reduction in intestinal and renal bile acid absorption. CONCLUSIONS: These coordinated events are mediated by increased muricholic acid levels which inhibit FXR signaling in favor of LXR and SREBP2 signaling to promote efficient fecal and urinary elimination of cholesterol and neo-synthesized bile acids. Therefore, our data suggest that enhancement of the hydrophilic bile acid pool following a cholesterol overload may contribute to the resistance to hypercholesterolemia in mice. This work paves the way for new therapeutic opportunities using hydrophilic bile acid supplementation to mitigate hypercholesterolemia.

[42] *Julve J, Escolà-Gil JC*. **High-Density Lipoproteins and Cardiovascular Disease: The Good, the Bad, and the Future**. International journal of molecular sciences 2021; 22.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34299108
ABSTRACT
Epidemiological, clinical, and experimental studies have shown that low levels of plasma high-density lipoprotein cholesterol (HDL-C) are associated with increased atherosclerotic cardiovascular disease (CVD) [...].

[43] *MacLeod C, Hadoke PWF, Nixon M*. **Glucocorticoids: Fuelling the Fire of Atherosclerosis or Therapeutic Extinguishers?** International journal of molecular sciences 2021; 22.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34299240
ABSTRACT
Glucocorticoids are steroid hormones with key roles in the regulation of many physiological systems including energy homeostasis and immunity. However, chronic glucocorticoid excess, highlighted in Cushing's syndrome, is established as being associated with increased cardiovascular disease (CVD) risk. Atherosclerosis is the major cause of CVD, leading to complications including coronary artery disease, myocardial infarction and heart failure. While the associations between glucocorticoid excess and increased prevalence of these complications are well established, the mechanisms underlying the role of glucocorticoids in development of atheroma are unclear. This review aims to better understand the importance of glucocorticoids in atherosclerosis and to dissect their cell-specific effects on key processes (e.g., contractility, remodelling and lesion development). Clinical and pre-clinical studies have shown both athero-protective and pro-atherogenic responses to glucocorticoids, effects dependent upon their multifactorial actions. Evidence indicates regulation of glucocorticoid bioavailability at the vasculature is complex, with local delivery, pre-receptor metabolism, and receptor expression contributing to responses linked to vascular remodelling and inflammation. Further investigations are required to clarify the mechanisms through which endogenous, local glucocorticoid action and systemic glucocorticoid treatment promote/inhibit atherosclerosis. This will

provide greater insights into the potential benefit of glucocorticoid targeted approaches in the treatment of cardiovascular disease.

[44] *Owusu J, Barrett E*. **Early Microvascular Dysfunction: Is the Vasa Vasorum a "Missing Link" in Insulin Resistance and Atherosclerosis**. International journal of molecular sciences 2021; 22.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34299190

ABSTRACT

The arterial vasa vasorum is a specialized microvasculature that provides critical perfusion required for the health of the arterial wall, and is increasingly recognized to play a central role in atherogenesis. Cardio-metabolic disease (CMD) (including hypertension, metabolic syndrome, obesity, diabetes, and pre-diabetes) is associated with insulin resistance, and characteristically injures the microvasculature in multiple tissues, (e.g., the eye, kidney, muscle, and heart). CMD also increases the risk for atherosclerotic vascular disease. Despite this, the impact of CMD on vasa vasorum structure and function has been little studied. Here we review emerging information on the early impact of CMD on the microvasculature in multiple tissues and consider the potential impact on atherosclerosis development and progression, if vasa vasorum is similarly affected.

[45] *Podbielska M, O'Keeffe J, Pokryszko-Dragan A*. **New Insights into Multiple Sclerosis Mechanisms: Lipids on the Track to Control Inflammation and Neurodegeneration**. International journal of molecular sciences 2021; 22.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34298940

ABSTRACT

Multiple sclerosis (MS) is a central nervous system disease with complex pathogenesis, including two main processes: immune-mediated inflammatory demyelination and progressive degeneration with axonal loss. Despite recent progress in our understanding and management of MS, availability of sensitive and specific biomarkers for these both processes, as well as neuroprotective therapeutic options targeted at progressive phase of disease, are still being sought. Given their abundance in the myelin sheath, lipids are believed to play a central role in underlying immunopathogenesis in MS and seem to be a promising subject of investigation in this field. On the basis of our previous research and a review of the literature, we discuss the current understanding of lipid-related mechanisms involved in active relapse, remission, and progression of MS. These insights highlight potential usefulness of lipid markers in prediction or monitoring the course of MS, particularly in its progressive stage, still insufficiently addressed. Furthermore, they raise hope for new, effective, and stage-specific treatment options, involving lipids as targets or carriers of therapeutic agents.

[46] *Wacinski P, Gadzinowski M, Dabrowski W et al.* **Anti-Inflammatory Effect of Very High Dose Local Vessel Wall Statin Administration: Poly(L,L-Lactide) Biodegradable Microspheres with Simvastatin for Drug Delivery System (DDS)**. International journal of molecular sciences 2021; 22.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34299106

ABSTRACT

Atherosclerosis involves an ongoing inflammatory response of the vascular endothelium and vessel wall of the aorta and vein. The pleiotropic effects of statins have been well described in many in vitro and in vivo studies, but these effects are difficult to achieve in clinical practice due to the low bioavailability of statins and their first-pass metabolism in the liver. The aim of this study was to test a

vessel wall local drug delivery system (DDS) using PLA microstructures loaded with simvastatin. Wistar rats were fed high cholesterol chow as a model. The rat vessels were chemically injured by repeated injections of perivascular paclitaxel and 5-fluorouracil. The vessels were then cultured and treated by the injection of several concentrations of poly(L,L-lactide) microparticles loaded with the high local HMG-CoA inhibitor simvastatin (0.58 mg/kg) concentration (SVPLA). Histopathological examinations of the harvested vessels and vital organs after 24 h, 7 days and 4 weeks were performed. Microcirculation in mice as an additional test was performed to demonstrate the safety of this approach. A single dose of SVPLA microspheres with an average diameter of 6.4 μm and a drug concentration equal to 8.1% of particles limited the inflammatory reaction of the endothelium and vessel wall and had no influence on microcirculation in vivo or in vitro. A potent pleiotropic (anti-inflammatory) effect of simvastatin after local SVPLA administration was observed. Moreover, significant concentrations of free simvastatin were observed in the vessel wall (compared to the maximum serum level). In addition, it appeared that simvastatin, once locally administered as SVPLA particles, exerted potent pleiotropic effects on chemically injured vessels and presented anti-inflammatory action. Presumably, this effect was due to the high local concentrations of simvastatin. No local or systemic side effects were observed. This approach could be useful for local simvastatin DDSs when high, local drug concentrations are difficult to obtain, or systemic side effects are present.

[47] *Bosso G, De Luca M, Alma G et al.* **ALERT-LDL: adherence to guidelines in the treatment of patients with dyslipidemia**. Internal and emergency medicine 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34302611

ABSTRACT

The association between LDL-c levels and cardiovascular outcomes suggests tailoring lipid-lowering therapies according to total cardiovascular risk. We aimed to evaluate the adherence to guidelines-oriented dyslipidaemia's treatment in an outpatient population referring to ARCA cardiologists, and assess the efficacy of treatment's optimization for each specific level of risk. Three thousand seventy-five patients enrolled in this prospective study were classified according to cardiovascular risk category, and their therapies were optimized. At the beginning and the 3 month follow-up visit, LDL-c data were collected, and further therapies were prescribed to the patients that did not reach the target. A significant LDL-c reduction was observed in all subgroups at different cardiovascular risk at the end of the study ($p<0.05$). The number of patients assuming statins, both in monotherapy and in combination with ezetimibe, increased during the follow-up (63% at the enrollment vs 89% after 12 months). At the enrollment, only 1.4% of patients were treated with PCSK-9 inhibitors while after 12 months the percentage increased both in high (5.8%) and very high-risk (18.4%) patients. At the beginning of the study, only 698/3075 patients (22.7%) reached lipid targets. At the end of the study, carried out by the referring cardiologists in the pertaining healthcare districts and specifically aimed to control the lipid profile, the percentage of patients on target increased in all risk categories (68.5%). Our results suggest carefully implementing measures that encourage outpatients and their cardiologists to achieve the targeted lipid profile according to cardiovascular risk.

[48] *Yu D, Wang Z, Zhang X et al.* **Remnant cholesterol and cardiovascular mortality in patients with type 2 diabetes and incident diabetic nephropathy**. The Journal of clinical endocrinology and metabolism 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34291804

ABSTRACT

PURPOSE: This study examined the association between remnant cholesterol (remnant-C) and cardiovascular mortality in patients with type 2 diabetes (T2D), chronic kidney disease (CKD) stages 3-5 and newly diagnosed diabetic nephropathy (DN). METHODS: This study determined the baseline lipid profile and searched for deaths with cardiovascular disease (CVD) within 2 years of baseline among 2282 adults enrolled between 01/01/2015 and 31/12/2016 who had T2D, CKD stages 3-5 and newly diagnosed DN. Adjusted Logistic regression models were used to assess the associations between lipid, especially remnant-C concentration (either as continuous or categorical variables), and risk of cardiovascular mortality. RESULTS: In multivariable-adjusted analyses, low-density lipoprotein cholesterol (LDL-C) (odds ratio [OR]:1.022; 95% confidence interval [CI]: 1.017-1.026, per 10mg/dl), HDL-C (0.929 [0.922-0.936], per 5 mg/dl), Non-HDL-C (1.024 [1.021-1.028], per 10mg/dl), and remnant-C (1.115 [1.103-1.127], per 10mg/dl), but not triglyceride were associated with cardiovascular mortality. Atherogenic dyslipidemia (triglycerides >150 mg/dl [1.69 mmol/l] and HDL-C <40 mg/dl in men or <50 mg/dl in women) was also associated with cardiovascular mortality (1.073[1.031-1.116]). Remnant-C ≥30 mg/dl differentiated patients at a higher risk of cardiovascular mortality compared with those with lower concentrations, especially with interaction with LDL-C level >100 mg/dl: the highest risk was found in patients with higher levels of both remnant-C and LDL-C (1.696 [1.613-1.783]). CONCLUSIONS: In patients with T2D, CKD stages 3-5 and incident DN, remnant-C was associated with higher risk of death with CVD. Different from the general population, the interaction of remnant-C and LDL-C was associated with the highest risk of cardiovascular mortality.

[49] *Kapoor K, Alfaddagh A, Stone NJ, Blumenthal RS*. **Update on the omega-3 fatty acid trial landscape: A narrative review with implications for primary prevention**. Journal of clinical lipidology 2021.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34294561

ABSTRACT

Residual risk mediated by hypertriglyceridemia among statin-treated individuals is an important clinical and public health challenge. Niacin, fibrates and omega-3 FA are three classes of non-statin agents with demonstrated TG-lowering effects. Randomized controlled trials of niacin and fibrates have been consistently negative, but the trial landscape for two key sources of omega-3 FAs, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) is more complex. Clinical trials evaluating omega-3 FA can be differentiated into those that studied mixed formulations (EPA + DHA) and those that studied EPA alone. Those assessing the impact of mixed formulations have not consistently demonstrated CVD risk reduction, whereas trials of EPA alone have been successful. Two recent trials of mixed formulations - STRENGTH (Long-Term Outcomes Study to Assess Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia) and OMEMI (Omega-3 fatty acids in Elderly patients with Myocardial Infarction) - studied contemporarily treated patients with mixed EPA + DHA formulations at higher doses than before and showed no benefit, thus adding valuable information to our overall understanding of this evolving therapeutic class. In this review, we contextualize the findings of STRENGTH and OMEMI within the existing omega-3 FA clinical trial landscape and look ahead to how future trials can inform existing knowledge gaps, particularly with regards to the applicability of these agents within the primary prevention realm.

[50] *Okutsu S, Kato Y, Funakoshi S et al.* **Effects of Weight Gain after 20 Years of Age and Incidence of Hyper-Low-Density Lipoprotein Cholesterolemia: The Iki Epidemiological Study of Atherosclerosis and Chronic Kidney Disease (ISSA-CKD)**. Journal of clinical medicine 2021; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34300264
ABSTRACT
The aim of this study was to investigate the effects of long-term weight gain from the age of 20 on incidence of hyper-low-density-lipoprotein (LDL) cholesterolemia in the general population of Japanese people. METHODS: We conducted a population-based retrospective cohort study using annual health checkup data for residents of Iki City, Nagasaki Prefecture, Japan. A total of 3179 adult (≥30 years old) men and women without hyper-LDL cholesterolemia at baseline, who underwent two or more health checkups were included in the analysis. Information on weight gain (≥10 kg) after 20 years of age was obtained using questionnaire. The outcome of this study was development of hyper-LDL cholesterolemia defined as LDL-cholesterol level ≥3.62 mmol/L and/or initiation of lipid-lowering medications. RESULTS: During a mean follow-up period of 4.53 years, 665 of the 3179 participants developed hyper-LDL cholesterolemia (46.5/1000 person-years). The incidence of hyper-LDL cholesterolemia was higher in participants with a weight gain of ≥10 kg (55.3/1000 person-years) than among those with a weight gain of <10 kg (41.8/1000 person-years). This association remained statistically significant even after adjustment for age, sex, smoking, daily drinking, exercise, obesity, hypertension, and diabetes (multivariable hazard ratio 1.31, 95% confidence interval 1.08-1.58, p = 0.006). CONCLUSION: A weight gain of ≥10 after 20 years of age affected the development of hyper-LDL cholesterol regardless of age, sex, and obesity in a general population of Japanese.

[51] *Tonetti DA, Desai SM, Nayar G et al.* **Symptomatic nonstenotic carotid disease: Evaluation of a proposed classification scheme in a prospective cohort**. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia 2021; 90:21-25.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34275551
ABSTRACT
INTRODUCTION: Unraveling symptomatic nonstenotic carotid disease (SyNC) as a stroke etiology from other cryptogenic stroke may have important implications for defining natural history and for tailoring secondary prevention strategies. We aim to describe the characteristics of the plaques in a prospectively-collected cohort of patients with non-invasive imaging suggesting symptomatic carotid stenosis but whose DSA demonstrated nonstenotic atheromatous disease, and to evaluate the recurrence rate depending on the type of SyNC. METHODS: We reviewed prospectively-collected data for patients presenting with new neurologic events and non-invasive imaging suggestive of moderate or severe (≥50%) carotid stenosis between July 2016 and October 2018. Patients were included in the present study if the degree of stenosis on DSA was < 50%. We assigned these patients into groups based on a previously-proposed working definition of SyNC, and analyzed the rate of recurrent stroke in the following 6 months. RESULTS: 28 patients had DSA-confirmed < 50% stenosis and constituted the study cohort. The median age was 73 years and 64% were male; median presenting NIHSS was 1 (IQR 0-3). The great majority (86%) of carotid plaques had high-risk features including ulcerated plaque (n = 21, 75%) and plaque > 3 mm thick (n = 18, 64%). 17 of 28 patients (61%) met classification criteria for "definite" or "probable" SyNC. Three of five patients in the "definite SyNC" group experienced recurrent neurologic events. CONCLUSION: The majority of

patients with non-invasive imaging suggesting carotid stenosis harbor symptomatic carotid disease per current classifications despite DSA stenosis < 50%. Current classification schema may allow for risk stratification of SyNC patients and these findings warrant further study.

[52] *Vine D, Proctor E, Weaver O et al.* **A Pilot Trial: Fish Oil and Metformin Effects on ApoB-Remnants and Triglycerides in Women With Polycystic Ovary Syndrome**. Journal of the Endocrine Society 2021; 5:bvab114.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34286169
ABSTRACT
CONTEXT: Women with polycystic ovary syndrome (PCOS) have increased incidence of atherogenic dyslipidemia and cardiovascular disease (CVD). Interventions targeting atherogenic dyslipidemia to reduce CVD risk are limited in women with PCOS. OBJECTIVE: This pilot study was conducted to determine the effect of 12 weeks of high dose fish oil (FO), metformin, and FO as an adjunct to metformin (FO-metformin) therapy on fasting and nonfasting plasma lipids and ApoB-remnants in young women with the metabolic syndrome (MetS) and PCOS. METHODS: In this open-label parallel pilot trial, women with MetS and PCOS (18-30 years of age) were randomized into 1 of 3 interventions: (1) FO; (2) metformin; and (3) FO-metformin. Plasma lipids and ApoB (48 and 100)-lipoproteins and triglycerides (TG) were measured in the fasted and postprandial state following a high-fat meal at baseline and postintervention. RESULTS: FO-metformin significantly lowered fasting plasma TG by >40% compared with FO and metformin treatments. Fasting plasma apoB48 was lowered 40% in FO-metformin and 15% in the FO groups from baseline to postintervention. ApoB48 area under the curve (ApoB48(AUC)), ApoB48 incremental AUC (ApoB48(iAUC)), ApoB100(AUC), and ApoB100(iAUC) decreased in all groups from baseline to postintervention; however, these findings did not reach statistical significance. CONCLUSION: The findings of this pilot trial show that high dose FO and FO-metformin combination therapy tend to lower fasting and postprandial plasma TG and ApoB-lipoprotein remnants compared with metformin; however, the study is limited by small sample size. These results may be clinically significant in individuals with PCOS for management of atherogenic dyslipidemia.

[53] *Jiang W, Hu JW, He XR et al.* **Statins: a repurposed drug to fight cancer**. Journal of experimental & clinical cancer research : CR 2021; 40:241.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34303383
ABSTRACT
As competitive HMG-CoA reductase (HMGCR) inhibitors, statins not only reduce cholesterol and improve cardiovascular risk, but also exhibit pleiotropic effects that are independent of their lipid-lowering effects. Among them, the anti-cancer properties of statins have attracted much attention and indicated the potential of statins as repurposed drugs for the treatment of cancer. A large number of clinical and epidemiological studies have described the anticancer properties of statins, but the evidence for anticancer effectiveness of statins is inconsistent. It may be that certain molecular subtypes of cancer are more vulnerable to statin therapy than others. Whether statins have clinical anticancer effects is still an active area of research. Statins appear to enhance the efficacy and address the shortcomings associated with conventional cancer treatments, suggesting that statins should be considered in the context of combined therapies for cancer. Here, we present a comprehensive review of the potential of statins in anti-cancer treatments. We discuss the current

understanding of the mechanisms underlying the anti-cancer properties of statins and their effects on different malignancies. We also provide recommendations for the design of future well-designed clinical trials of the anti-cancer efficacy of statins.

[54] *Kefer J, Chenu P, Gurné O et al.* **Reduction of Lipid-Core Burden Index in Nonculprit Lesions at Follow-Up after ST-Elevation Myocardial Infarction: A Randomized Study of Bioresorbable Vascular Scaffold versus Optimal Medical Therapy**. J Interv Cardiol 2021; 2021:5590093.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34290573
ABSTRACT
BACKGROUND: Non-flow-limiting nonculprit lesions (NCL) that contain a large lipid-rich necrotic core (nonculprit lipid-rich plaques (NC-LRP)) are most likely to cause recurrent acute coronary syndrome after ST-elevation myocardial infarction (STEMI). Near-infrared spectroscopy (NIRS) detects LRPs using the maximum 4 mm lipid-core burden index (maxLCBI(4 mm)). Few data are available regarding NIRS-guided therapy of these NC-LRPs, which are a potential target for preventive stenting. Bioresorbable vascular scaffold (BVS) provides local drug delivery and could facilitate plaque passivation after resorption. This study sought to assess the safety of BVS implantation in NC-LRPs and its efficacy in reducing maxLCBI(4 mm) at 2-year follow-up after STEMI. METHODS AND RESULTS: In total, 33 non-flow-limiting NCLs from 29 STEMI patients were included in this study. Of these, 15 were LRPs and were randomly assigned to either the BVS + optimal medical therapy (OMT) arm (group 1; N = 7) or the OMT arm (group 2; N = 8). At baseline, there were no differences in plaque characteristics between groups (fractional flow reserve: 0.85 ± 0.04 vs. 0.89 ± 0.06; diameter stenosis (DS): 43.4 ± 8 vs. 40.1 ± 10.7%; plaque burden 54.98 ± 5.8 vs. 49.76 ± 8.31%; and maxLCBI(4 mm) 402 [348; 564] vs. 373 [298; 516]; p=NS for all comparisons between groups 1 and 2, respectively). Seven BVSs were implanted 3 ± 1 days after STEMI in six patients, without complications. At angiographic follow-up (712 [657; 740] days), a significant and similar reduction of maxLCBI(4 mm) was observed in both groups, with a median change of 306 [257; 377] in group 1 vs. 300 [278; 346] in group 2 (p=0.44). DS was significantly lower in group 1 vs. group 2 (19.8 ± 7 vs. 41.7 ± 13%, p=0.003), while plaque burden remained unchanged in both groups. Overall survival was 100%, target lesion failure was 13%, and stent thrombosis was 0%. CONCLUSIONS: BVS + OMT and OMT appear as similarly safe and effective in reducing maxLCBI(4mm) in NC-LRPs at 2-year follow-up after STEMI.

[55] *El Khoudary SR, Nasr A, Matthews KA et al.* **Associations of HDL metrics with coronary artery calcium score and density among women traversing menopause**. Journal of lipid research 2021; 62:100098.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34303684
ABSTRACT
The cardioprotective association of high-density lipoprotein cholesterol (HDL-C) may vary by menopause stage or estradiol level. We tested whether associations of comprehensive HDL metrics (HDL subclasses, phospholipid and triglyceride content, and HDL cholesterol efflux capacity [HDL-CEC]) with coronary artery calcium (CAC) score and density vary by menopause stage or estradiol level in women transitioning through menopause. Participants (N = 294; mean age [SD]: 51.3 [2.9]) had data on HDL metrics and CAC measures at one or two time points during the menopause transition. Generalized estimating equations were used for analyses. Effect modifications by

menopause stage or estradiol level were tested in multivariable models. In adjusted models, menopause stage modified the associations of specific HDL metrics with CAC measures. Higher small HDL particles (HDL-P) concentrations (p-interaction = 0.008) and smaller HDL size (p-interaction = 0.02) were associated with greater odds of CAC presence in late perimenopause than in pre/early perimenopause stage. Women in the highest estradiol tertile, but not the lower tertiles, showed a protective association of small HDL-P with CAC presence (p-interaction = 0.007). Lower large HDL-P concentrations (p-interaction = 0.03) and smaller HDL size (p-interaction = 0.03) were associated with lower CAC density in late perimenopause than in postmenopause stage. Associations of HDL phospholipid and triglyceride content and HDL-CEC with CAC measures did not vary by menopause stage or estradiol level. We concluded that HDL subclasses may impact the likelihood of CAC presence and the stability of coronary plaque differently over the menopause transition. Endogenous estradiol levels may contribute to this observation.

[56] *François M, Thédrez A, Garçon D et al.* **PCSK9 is not secreted from mature differentiated intestinal cells**. Journal of lipid research 2021:100096.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34280453
ABSTRACT
Proprotein convertase subtilisin/kexin type 9 (PCSK9) promotes lysosomal degradation of the LDL receptor and is a key regulator of cholesterol metabolism. After the liver, the small intestine is the second organ that highly expresses PCSK9. However, the small intestine's ability to secrete PCSK9 remains a matter of debate. While liver-specific PCSK9-deficient mice present no PCSK9 in systemic blood, human intestinal Caco-2 cells can actively secrete PCSK9. This raises the possibility for active intestinal secretion via the portal blood. Here we aimed to determine whether enterocytes can secrete PCSK9 using in vitro, ex vivo and in vivo approaches. We first observed that PCSK9 secretion from Caco-2 cells was biphasic and dependent on Caco-2 maturation status. Transcriptional analysis suggested that this transient reduction in PCSK9 secretion might be due to loss of SREBP2-mediated transcription of PCSK9. Consistently, PCSK9 secretion was not detected ex vivo in human or mouse intestinal biopsies mounted in Ussing chambers. Finally, direct comparison of systemic versus portal blood PCSK9 concentrations in wild-type or liver-specific PCSK9-deficient mice confirmed the inability of the small intestine to secrete PCSK9 into the portal compartment. Altogether, our data demonstrate that mature enterocytes do not secrete PCSK9 and reinforce the central role of the liver in the regulation the concentration of circulating PCSK9 and consequently of cellular LDL receptors.

[57] *Sun X, Bee YM, Lam SW et al.* **Effective Treatment Recommendations for Type 2 Diabetes Management Using Reinforcement Learning: Treatment Recommendation Model Development and Validation**. Journal of medical Internet research 2021; 23:e27858.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34292166
ABSTRACT
BACKGROUND: Type 2 diabetes mellitus (T2DM) and its related complications represent a growing economic burden for many countries and health systems. Diabetes complications can be prevented through better disease control, but there is a large gap between the recommended treatment and the treatment that patients actually receive. The treatment of T2DM can be challenging because of different comprehensive therapeutic targets and individual variability of the patients, leading to the need for precise, personalized treatment. OBJECTIVE: The aim of this study was to develop

treatment recommendation models for T2DM based on deep reinforcement learning. A retrospective analysis was then performed to evaluate the reliability and effectiveness of the models. METHODS: The data used in our study were collected from the Singapore Health Services Diabetes Registry, encompassing 189,520 patients with T2DM, including 6,407,958 outpatient visits from 2013 to 2018. The treatment recommendation model was built based on 80% of the dataset and its effectiveness was evaluated with the remaining 20% of data. Three treatment recommendation models were developed for antiglycemic, antihypertensive, and lipid-lowering treatments by combining a knowledge-driven model and a data-driven model. The knowledge-driven model, based on clinical guidelines and expert experiences, was first applied to select the candidate medications. The data-driven model, based on deep reinforcement learning, was used to rank the candidates according to the expected clinical outcomes. To evaluate the models, short-term outcomes were compared between the model-concordant treatments and the model-nonconcordant treatments with confounder adjustment by stratification, propensity score weighting, and multivariate regression. For long-term outcomes, model-concordant rates were included as independent variables to evaluate if the combined antiglycemic, antihypertensive, and lipid-lowering treatments had a positive impact on reduction of long-term complication occurrence or death at the patient level via multivariate logistic regression. RESULTS: The test data consisted of 36,993 patients for evaluating the effectiveness of the three treatment recommendation models. In 43.3% of patient visits, the antiglycemic medications recommended by the model were concordant with the actual prescriptions of the physicians. The concordant rates for antihypertensive medications and lipid-lowering medications were 51.3% and 58.9%, respectively. The evaluation results also showed that model-concordant treatments were associated with better glycemic control (odds ratio [OR] 1.73, 95% CI 1.69-1.76), blood pressure control (OR 1.26, 95% CI, 1.23-1.29), and blood lipids control (OR 1.28, 95% CI 1.22-1.35). We also found that patients with more model-concordant treatments were associated with a lower risk of diabetes complications (including 3 macrovascular and 2 microvascular complications) and death, suggesting that the models have the potential of achieving better outcomes in the long term. CONCLUSIONS: Comprehensive management by combining knowledge-driven and data-driven models has good potential to help physicians improve the clinical outcomes of patients with T2DM; achieving good control on blood glucose, blood pressure, and blood lipids; and reducing the risk of diabetes complications in the long term.

[58] *Ceacareanu AC, Jolly SD, Nimako GK, Wintrob ZAP*. **Statin Type and Cancer Outcomes in Patients with Diabetes Type 2 and Solid Tumors**. Journal of research in pharmacy practice 2021; 10:50-56.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34295853
ABSTRACT
OBJECTIVE: Type 2 diabetes mellitus (T2DM) affects 10% of Americans and is associated with an increased incidence of cancer. Statins are first-line cholesterol-lowering medications in the treatment of hyperlipidemia. Several studies have demonstrated a relationship between statin use and reduced cancer incidence. We examined the cancer benefits of statin subtypes, with specific attention to disease-free survival (DFS) and overall survival (OS). METHODS: This retrospective review included adults with T2DM diagnosed with solid tumors at Roswell Park Cancer Institute in Buffalo, NY, USA (2003-2010). Individuals with gestational diabetes, incomplete records, or diagnosed with rare solid tumors were excluded. Follow-up began at the date of diagnosis and ended with the first confirmed

recurrence, death, or loss of contact. Demographics were assessed by Chi-square, Kaplan-Meier survival analyses, and Cox proportional hazards regression. FINDINGS: Overall, 1102 patients met inclusion criteria, 52.1% of the study participants were female, and 578 participants (52.5%) died during the follow-up period which ranged from 0 to 156 months. Hydrophilic statin use was associated with improved DFS at 5-year follow-up (41.0% vs. 36.9%, P = 0.0077) compared to lipophilic statin use. Multivariate regression revealed that hydrophilic statins were associated with improved DFS (hazard ratio [HR]: 0.706, 95% confidence interval [CI]: 0.526-0.947) and OS (HR: 0.685, 95% CI: 0.503-0.934). Pravastatin was associated with improved OS (HR: 0.674, 95% CI: 0.471-0.964). CONCLUSION: In patients with T2DM and cancer, hydrophilic statins, and pravastatin in particular, are associated with improved DFS as well as OS. Further research examining the cancer-specific effects of hydrophilic and lipophilic statins is needed to better understand their beneficial effects.

[59] *Cuomo G, Raimondi A, Rivasi M et al.* **Adherence to Lipid-Lowering Medication in People Living with HIV: An Outpatient Clinic Drug Direct Distribution Experience**. Journal of research in pharmacy practice 2021; 10:10-16.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34295847
ABSTRACT
OBJECTIVE: Adherence to lipid-lowering drugs could be challenging in our patients as it is in the general population, which is described as low as 25%. Our aim was to evaluate adherence to statins and to investigate clinical event impact on it. METHODS: This retrospective study on HIV+ patients attending to Clinic of Modena (Italy) was conducted in order to evaluate characteristics, clinical events, and adherence on lipid-lowering drugs. All drugs for comorbidities are distributed by the hospital pharmacy and recorded in an electronical database. Adherence was also evaluated in patients who were supplied with antilipemics in external pharmacies through phone calls. Patients were considered adherent if the percentage of correct time of drug refill was >80%. FINDINGS: Totally 1123 patients were evaluated. Lipid-lowering drugs (statins, fenofibrate, and omega-3 oil) were prescribed in 242 patients (21.5%). Prescription occurred mainly in those who were older, males, and Italians. Two hundred of them (82.6%) used statins alone, 23 (9.5%) only fenofibrate or omega-3 oil, and 19 (7.8%) a combination of both drugs. The median adherence was 90% while patients with adherence >80% resulted 153 (63.2%). Forty-six (19%) had a clinical history of cardiovascular events; 59% of them, placed in secondary prophylaxis, and 76%, already in treatment, continued to adhere. No differences in terms of adherence according to the type of drug distribution (hospital pharmacy or outside pharmacies) were found. CONCLUSION: Linking the supply of these drugs to that of antiretrovirals led to a good level of adherence higher than that described in the general population. The majority of the patients who experienced a cardiovascular event remain adherent to the prescribed therapy.

[60] *Wilkins JT, Lloyd-Jones DM*. **Novel Lipid-Lowering Therapies to Reduce Cardiovascular Risk**. Jama 2021; 326:266-267.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34283191
ABSTRACT

[61] *Wang S*. **Association between serum low-density lipoprotein cholesterol and metabolic syndrome in a working population**. Lipids in health and disease 2021; 20:73.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34275455

ABSTRACT

BACKGROUND: The studies, investigating the association of low-density lipoprotein cholesterol (LDL-C) with metabolic syndrome (MetS) are limited with controversial conclusions. Therefore, this study aimed at revealing the specific relationship between the serum LDL-C levels and MetS prevalence in a large working population. METHODS: Secondary data analysis of a cross-sectional study, conducted between 2012 and 2016 in Spain on participants aged within the range of 20-70 years, involved 60,799 workers. Logistic regression analysis was applied to evaluate the association between the levels of serum LDL-C and MetS prevalence. RESULTS: Among the 60,799 workers, the prevalence of MetS was 9.0%. The odds ratios (95% confidence intervals) of MetS prevalence were 1.27 (1.16-1.39) and 1.53 (1.41-1.65) for the individuals with the LDL-C levels in lower (<103.8 mg/dL) and upper (>135.8 mg/dL) tertiles as compared to those with the LDL-C levels in middle tertile (103.8-135.8 mg/dL) in the studied population. Similarly, a U-shaped relationship was also observed in male cohort. The serum LDL-C levels associated with the lowest risk of current MetS were 113.6 mg/dL and 117.6 mg/dL in the overall studied population and male cohort, respectively. The female workers with the levels of LDL-C higher than 135.0 mg/dL had an increased prevalence of MetS (P<0.05). CONCLUSIONS: The low and high levels of serum LDL-C were associated with an increased prevalence of MetS in the working population and in male workers. Only the high (>135.0 mg/dL) levels of LDL-C increased MetS prevalence in female workers.

[62] *Noble C, Carlson K, Neumann E et al.* **Ex Vivo Evaluation of IVUS-VH Imaging and the Role of Plaque Structure on Peripheral Artery Disease**. Med Nov Technol Devices 2020; 8.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34291202

ABSTRACT

Peripheral artery disease (PAD) results from the buildup of atherosclerotic plaque in the arterial wall, can progress to severe ischemia and lead to tissue necrosis and limb amputation. We evaluated a means of assessing PAD mechanics ex vivo using ten human peripheral arteries with PAD. Pressure-inflation testing was performed at six physiological pressure intervals ranging from 10-200 mmHg. These vessels were imaged with IVUS-VH to determine plaque composition and change in vessel structure with pressure. Statistical analysis was performed to determine which plaque structures and distributions of these structures had the greatest influence on wall deformation. We found that fibrous plaque, necrotic core, and calcification had a statistically significant effect on all variables ($p<0.05$). The presence of large concentrations of fibrous plaque was linked to reduced vessel compliance and ellipticity, which could lead to stent fractures and restenosis. For the plaque distribution we found that clustered necrotic core increased overall compliance while clustered calcification decreased overall compliance. The effect of plaque distribution on vessel wall deformation must be considered equally important to plaque concentration.

[63] *Diaz EC, Weber JL, Adams SH et al.* **Cardiorespiratory Fitness Associates with Blood Pressure and Metabolic Health of Children-The Arkansas Active Kids Study**. Med Sci Sports Exerc 2021.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34280939

ABSTRACT

INTRODUCTION: High blood pressure (HBP) in children causes pre-clinical damage to the heart and accelerates atherosclerosis. Current pharmacological treatments have limited ability to prevent end-organ damage, particularly that of the kidneys. A contrasting element between adult vs. pediatric HPB treatment, is the emphasis in adults on exercise regimens that target increments in cardiorespiratory fitness [CRF, (peak VO2)]. The aim of this study was to evaluate the association of CRF with blood pressure percentiles and blood pressure status in children with normal and excessive adiposity (NA vs. EA). An exploratory aim was to measure associations of CRF with a) other cardiovascular disease risk factors commonly found in children with HBP, and b) kidney function. METHODS: Children (n= 211), attended one study visit. CRF was measured using an incremental bike test, and body composition by dual-energy X-ray absorptiometry. Fat-free mass (FFM) index was calculated as kilograms of fat-free mass per square meter. Multiple logistic and linear regression analyses were used to model the probability of HBP, and other variables of interest [plasma lipids, HOMA2-IR, ALT, and glomerular filtration rate (eGRF)] against peak VO2. RESULTS: CRF interacted with adiposity status in predicting the probability of HBP. Each additional milliliter per minute per FFMI in peak VO2 decreased the odds of HBP by 8% in the EA group only (OR= 0.92; CI= 0.87-0.99). Systolic and diastolic blood pressure percentiles decreased, and eGFR increased with increasing CRF in both adiposity-level groups. HOMA2-IR and ALT decreased with increasing CRF in children with EA only. CONCLUSIONS: Higher CRF associated with decreased probability of clinical HBP, lower insulin resistance, and improved liver function in children with EA. Yet, blood pressure percentiles and kidney function improved with increasing CRF irrespective of adiposity status.

[64] *Murphy AJ, Febbraio MA*. **Immune-based therapies in cardiovascular and metabolic diseases: past, present and future**. Nature reviews. Immunology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34285393
ABSTRACT
Cardiometabolic disorders were originally thought to be driven primarily by changes in lipid metabolism that cause the accumulation of lipids in organs, thereby impairing their function. Thus, in the setting of cardiovascular disease, statins - a class of lipid-lowering drugs - have remained the frontline therapy. In the past 20 years, seminal discoveries have revealed a central role of both the innate and adaptive immune system in driving cardiometabolic disorders. As such, it is now appreciated that immune-based interventions may have an important role in reducing death and disability from cardiometabolic disorders. However, to date, there have been a limited number of clinical trials exploring this interventional strategy. Nonetheless, elegant preclinical research suggests that immune-targeted therapies can have a major impact in treating cardiometabolic disease. Here, we discuss the history and recent advancements in the use of immunotherapies to treat cardiometabolic disorders.

[65] *Nurmohamed NS, Stroes ESG*. **Working towards full eradication of lipid-driven cardiovascular risk?** Neth Heart J 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34279797
ABSTRACT
Lipid-driven cardiovascular disease (CVD) risk is caused by atherogenic apolipoprotein B (apoB) particles containing low-density lipoprotein cholesterol (LDL-C), triglycerides and lipoprotein(a) [Lp(a)] and resembles a large and modifiable proportion of the total CVD risk. While a surplus of novel lipid-

lowering therapies has been developed in recent years, management of lipid-driven CVD risk in the Netherlands remains suboptimal. To lower LDL-C levels, statins, ezetimibe and proprotein convertase subtilisin/kexin type 9 inhibiting antibodies are the current standard of therapy. With the approval of bempedoic acid and the silencing RNA inclisiran, therapeutic options are expanding continuously. Although the use of triglyceride-lowering therapies remains a matter of debate, post hoc analyses consistently show a benefit in subsets of patients with high triglyceride or low high-density lipoprotein cholesterol levels. Pemafibrate and novel apoC-III could be efficacious options when approved for clinical use. Lp(a)-lowering therapies such as pelacarsen are under clinical investigation, offering a potent Lp(a)-lowering effect. If proven effective in reducing cardiovascular endpoints, Lp(a) lowering holds promise to be the third axis of effective lipid-lowering therapies. Using these three components of lipid-lowering treatment, the contribution of apoB-containing lipid particles to the CVD risk may be fully eradicated in the next decade.

[66] *Zhang M, Wu S, Xu S, Chen S*. **Impact of monocyte to high-density lipoprotein ratio on the identification of prevalent coronary heart disease: insights from a general population**. Postgraduate medicine 2021:1-8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34281466
ABSTRACT
BACKGROUND: Recent studies have identified monocyte to high-density lipoprotein ratio (MHR) as a simple, practical surrogate of atherosclerosis. Considering atherosclerosis is a major mechanism of coronary heart disease (CHD). The present study aims to evaluate the association between MHR and the prevalence of CHD. METHODS AND RESULTS: The present cross-sectional work included 6442 participants (mean age: 59.57 years, 60.2% females), all of them were included from rural areas of northern China between October 2019 to April 2020. MHR was acquired as monocytes count divided by high-density lipoprotein concentration. Prevalent CHD researched 3.14%. After adjustment of sex, age, current drinking and smoking, BMI, WC, diabetes, hypertension, LDL-C, TG, eGFR, lipid-lowering therapy and cerebrovascular disease history, each standard deviation increase of MHR cast a 39.5% additional CHD risk. Furthermore, the top quartile of MHR had an additional 89.0% CHD risk than the bottom quartile. Besides, smooth curve fitting revealed a linear pattern of the association. Additionally, the stratified evaluation showed a robust correlation among the subgroups divided by CHD risk factors. Finally, area under the curve demonstrated an advancement when including MHR into common CHD risk factors (0.744 vs 0.761, $p < 0.001$). Consistently, reclassification analysis indicated the improvement from MHR (all $P = 0.003$). CONCLUSION: Our work suggests the robust and linear relationship between MHR and the prevalent CHD in a general population, providing epidemiological evidence for laboratory studies. More importantly, the findings implicate the efficacy of MHR to be a potential indicator to identify the prevalent CHD.

[67] *Bonfiglio CA, Weber C, Atzler D, Lutgens E*. **Immunotherapy and cardiovascular diseases (CVD): novel avenues for immunotherapeutic approaches**. QJM : monthly journal of the Association of Physicians 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34293177
ABSTRACT
As current therapies for cardiovascular disease (CVD), predominantly based on lipid lowering, still face an unacceptable residual risk, novel treatment strategies are being explored. Besides lipids,

inflammatory processes play a major role in the pathogenesis of atherosclerosis, the underlying cause of the majority of CVD. The first clinical trials targeting the interleukin-1β-inflammasome axis have shown that targeting this pathway is successful in reducing cardiovascular events but did not decrease overall CVD mortality. Hence, novel and improved immunotherapeutics to treat CVD are being awaited. In this review we highlight novel immunotherapeutic approaches in CVD as well as future challenges ahead.

[68] *Krasteva MP, Müller MD, Pilgram-Pastor SM, Heldner MR*. **[Atherosclerosis of the intracranial arteries and of the extracranial carotid artery.]**. Ther Umsch 2021; 78:277-289.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34291662
ABSTRACT
Atherosclerosis of the intracranial arteries and of the extracranial carotid artery. Abstract. Intracranial atherosclerotic stenoses are the most common cause of ischemic stroke worldwide. Nowadays, three therapeutic approaches are available for consideration for patients with intracranial atherosclerotic stenoses: A conservative therapy (best medical treatment, management of vascular risk factors and healthy lifestyle), endovascular and surgical therapy. Conservative approach has been recommended for patients with asymptomatic intracranial atherosclerotic stenoses, as well as for those with symptomatic stenoses. Endovascular therapy should be considered as a treatment option for carefully selected patients with recurrent ischemic strokes attributed to the stenotic artery while receiving best medical therapy. Surgical revascularisation is rarely favored in patients with intracranial stenoses. In patients with extracranial atherosclerotic stenoses, carotid endarterectomy (CEA) has been associated with a lower risk of death and recurrent stroke when compared to carotid angioplasty and stenting (CAS). Especially in elderly patients over 70 years of age CEA is preferred over CAS due to the twofold increased 30-day risk of recurrent stroke or death in patients treated with CAS. Results from contemporary studies using modern techniques and devices are expected. It remains unclear whether patients with asymptomatic extracranial atherosclerotic stenoses receiving best medical treatment would benefit of invasive procedures such as CEA or CAS.

[69] *Karásek D*. **Biologic therapy for dyslipidemia**. Vnitr Lek 2021; 67:206-211.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34275305
ABSTRACT
Dyslipidemia treatment represents a very dynamically growing segment of pharmacotherapy, including a production of biological agents. Nowadays, they are targeting at various proteins that are involved in the synthesis, transport, or metabolism of lipoproteins. This review provides a statement of current options for the biological treatment of dyslipidemias and for other products that have the potential to broaden its spectrum in the near future.

[70] *Machaczka O, Homza M, Macounová P et al.* **Assessment of toe brachial index validity in diabetic patients - interim results**. Vnitr Lek 2021; 67:3-8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34275312
ABSTRACT
INTRODUCTION: The toe brachial index (TBI) is recommended for the detection of lower extremity arterial disease (LEAD) in case of reduced efficacy of the ankle brachial index (ABI), which most often occurs in diabetics. In this case, TBI is expected to give more accurate results. There are not many

studies dealing with the use of TBI specifically in diabetics and the results are different. OBJECTIVE: The purpose of this work is to present the interim results of the study, whose main objective is to assess the validity of TBI in diabetics and to determine whether this method provides improvements over the ABI. METHODS: In the first phase of the study, 42 limbs were examined in 21 patients with type 2 diabetes. ABI was measured using the automatic oscillometric method (ABI OSC) and the manual method using the pencil doppler (ABI DPP). TBI was determined using an automatic plethysmographic method. The reference examination of the arteries of the lower limbs was performed using duplex ultrasonography (DUS). A paired t-test was used to compare the individual TBI and ABI methods. Cut-off points ABI < 0.9; TBI < 0.7; and DUS stenosis > 50 % were used to evaluate validity parameters. RESULTS: The individual ABI and TBI methods gave different results (p < 0.05). In eight limbs of the total number, LEAD was demonstrated using DUS. The best validity parameters were demonstrated by the TBI - sensitivity 0.88; specificity 0.88; positive predictive value 0.64; negative predictive value 0.97, positive likelihood ratio 7.44; negative likelihood ratio 0.14. The ABI method of calculation, that uses lower systolic blood pressure determined from two measurement sites on the ankle as a numerator, had a higher validity parameters. The ABI OSC did not correctly detect a single limb with stenosis > 50 % in this cohort. CONCLUSION: According to the interim results of this work, the TBI was more suitable for the detection of LEAD in diabetics in comparison with ABI.

[71] *Nussbaumerová B*. **An effective communication between the physician and the patient in an early intervention of hypertension and dyslipidemia**. Vnitr Lek 2021; 67:244-248.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34275311

ABSTRACT

The article summarizes the cornestones of inicitating the pharmacotherapy of hypertension and dyslipidemia. The intervention of dyslipidemia should not be delayed after the intervention of hypertension. The compliance and the adhrence are far from ideal. The physicians should support their patients with an appropriate approach. Vascular age should be used for the explanation of the cardiovascular risk.