Literature update week 21 (2018)

[1] *Girerd X, Hanon O, Vaisse B*. **[Use of the EvalObs((R)) adherence scale in an unselected French population of treated subjects with antihypertensive, hypolipemiants or oral antidiabetics medications: The FLAHS 2017 adherence survey]**. Annales de cardiologie et d'angeiologie 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29786508
ABSTRACT
OBJECTIVE: A Visual Analog Scale (VAS) is useful for diagnosing medication nonadherence and its validity has been evaluated using electronic pillbox as the gold standard. We have developed the EvaLobs((R)) scale for use on paper or on smartphone and the aim of the study was to administrate the scale among FLAHS 2017 participants treated for an hypertension, a dyslipidemia or diabetes. In subjects treated with antihypertensive medications, participants completed the 6-item Girerd Scale and EvaLobs((R)). METHODS: The French League Against Hypertension Survey (FLAHS) are carried out by self-questionnaire sent by mail to individuals from the French Kantar Health sampling frame (representative panel of the population living in metropolitan France). In 2017, FLAHS was conducted in 4783 subjects aged 35 and over. The EvaLobs((R)) has a scale from 0 to 15 and the use instruction is "how many days have you taken the drug in the past 15 days". A score>12 indicates a "good compliance". The 6-item Girerd scale was also completed. "Good adherence" was determined for a score of 0 to 2 and "nonadherence" for a score of 3 or more. The agreement between EvaLobs((R)) and the 6-item Girerd scale was evaluated in treated hypertensives. RESULTS: The survey included 4783 subjects with 1308 treated hypertensives, 942 subjects treated with lipid-lowering drugs and 405 subjects treated with anti-diabetics. EVALOBS((R)) indicates "Good adherence" in 96% of subjects and the 6 questions questionnaire indicates "good adherence" in 95% of subjects. An excellent agreement is noted in 93.8%. An EvaLobs((R)) score indicating nonadherence or an absence of response to EvaLobs((R)) is observed in 3.6% [CI 95, 2.5-4.7] of hypertensives, in 6.0% [CI 95, 3.9-8.1] of diabetics and in 8.2% [CI 95, 6.5-9.9] of dyslipidemic patients. CONCLUSION: In the population living in France and in unselected patients treated for metabolic disease or hypertension, non-adherence is lowest for antihypertensive medications and highest for statins. EvaLobs((R)), which shows good agreement with an adherence questionnaire, is a quick and simple tool for assessing adherence. The smartphone app EvaLobs((R)) is available for free on Google play and the Apple store.

[2] *Colombo M, Looker HC, Farran B et al.* **Apolipoprotein CIII and N-terminal prohormone b-type natriuretic peptide as independent predictors for cardiovascular disease in type 2 diabetes**. Atherosclerosis 2018; 274:182-190.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29793175
ABSTRACT
BACKGROUND AND AIMS: Developing sparse panels of biomarkers for cardiovascular disease in type 2 diabetes would enable risk stratification for clinical decision making and selection into clinical trials. We examined the individual and joint performance of five candidate biomarkers for incident cardiovascular disease (CVD) in type 2 diabetes that an earlier discovery study had yielded. METHODS: Apolipoprotein CIII (apoCIII), N-terminal prohormone B-type natriuretic peptide (NT-proBNP), high sensitivity Troponin T (hsTnT), Interleukin-6, and Interleukin-15 were measured in baseline serum samples from the Collaborative Atorvastatin Diabetes trial (CARDS)

of atorvastatin versus placebo. Among 2105 persons with type 2 diabetes and median age of 62.9 years (range 39.2-77.3), there were 144 incident CVD (acute coronary heart disease or stroke) cases during the maximum 5-year follow up. We used Cox Proportional Hazards models to identify biomarkers associated with incident CVD and the area under the receiver operating characteristic curves (AUROC) to assess overall model prediction. RESULTS: Three of the biomarkers were singly associated with incident CVD independently of other risk factors; NT-proBNP (Hazard Ratio per standardised unit 2.02, 95% Confidence Interval [CI] 1.63, 2.50), apoCIII (1.34, 95% CI 1.12, 1.60) and hsTnT (1.40, 95% CI 1.16, 1.69). When combined in a single model, only NT-proBNP and apoCIII were independent predictors of CVD, together increasing the AUROC using Framingham risk variables from 0.661 to 0.745. CONCLUSIONS: The biomarkers NT-proBNP and apoCIII substantially increment the prediction of CVD in type 2 diabetes beyond that obtained with the variables used in the Framingham risk score.

[3] *Feng T, Liu P, Wang X et al.* **SIRT1 activator E1231 protects from experimental atherosclerosis and lowers plasma cholesterol and triglycerides by enhancing ABCA1 expression**. Atherosclerosis 2018; 274:172-181.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29787963
ABSTRACT
BACKGROUND AND AIMS: Sirtuin 1 (SIRT1) is a nicotinamide adenine dinucleotide-dependent protein deacetylase. Recent studies have demonstrated that enhancing SIRT1 expression or activity may modulate cholesterol and lipid metabolism. However, pharmacological and molecular regulators for SIRT1 are scarce. Here, we aimed to find novel small molecule modulators of SIRT1 to regulate cholesterol and lipid metabolism. METHODS: A high-throughput screening assay was established to identify SIRT1 activators. Surface plasmon resonance and immunoprecipitation were performed to confirm the interaction of E1231 with SIRT1. Cholesterol assay was performed to demonstrate the in vitro effect of E1231. The in vivo effect of E1231 was evaluated in experimental models. RESULTS: E1231, a piperazine 1,4-diamide compound, was identified as a SIRT1 activator with EC50 value of 0.83muM. E1231 interacted with recombinant human SIRT1 protein and deacetylated liver X receptor-alpha (LXRalpha). E1231 increased ATP-binding cassette transporter A1 (ABCA1) expression in RAW 264.7cells dependent on SIRT1 and LXRalpha. E1231 promoted cholesterol efflux and inhibited lipid accumulation in RAW 264.7cells via SIRT1 and ABCA1. In the golden hamster hyperlipidemia model, E1231 treatment decreased total cholesterol and triglyceride levels in both serum and the liver, while increased cholesterol content in feces. Moreover, E1231 increased ABCA1 and SIRT1 protein expression in the liver. In ApoE(-/-) mice, E1231 treatment reduced atherosclerotic plaque development compared with untreated ApoE(-/-) mice. CONCLUSIONS: We identified a novel SIRT1 activator E1231 and elucidated its beneficial effects on lipid and cholesterol metabolism. Our study suggests that E1231 might be developed as a novel drug for treating atherosclerosis.

[4] *Montefusco DJ, Allegood JC, Spiegel S, Cowart LA*. **Non-alcoholic fatty liver disease: Insights from sphingolipidomics**. Biochem Biophys Res Commun 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29778532
ABSTRACT

Literature update week 21 (2018)

Non-alcoholic fatty liver disease (NAFLD) is a major clinical concern and its treatment consumes abundant resources. While accumulation of lipids in hepatocytes initiates the disease, this in itself is not necessarily harmful; rather, initiation of inflammation and subsequent fibrosis and cirrhosis are critical steps in NAFLD pathology. Mechanisms linking lipid overload to downstream disease progression are not fully understood; however, bioactive lipid metabolism may underlie instigation of proinflammatory signaling. With the advent of high-throughput, sensitive, and quantitative mass spectrometry-based methods for assessing lipid profiles in NAFLD, several trends have emerged, including that increases in specific sphingolipids correlate with the transition from the relatively benign condition of simple fatty liver to the much more concerning inflamed state. Continued studies that implement sphingolipid profiling will enable the extrapolations of candidate enzymes and pathways involved in NAFLD, either in biopsies or plasma from human samples, and also in animal models, from which data are much more abundant. While most data thus far are derived from targeted lipidomics approaches, unbiased, semi-quantitative approaches hold additional promise for furthering our understanding of sphingolipids as markers of and players in NAFLD.

[5] *Bhadoriya A, Sanyal M, Shah PA, Shrivastav PS*. **Simultaneous quantitation of rosuvastatin and ezetimibe in human plasma by LC-MS/MS: Pharmacokinetic study of fixed-dose formulation and separate tablets**. Biomedical chromatography : BMC 2018:e4291.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29782035
ABSTRACT
A simple, high-throughput and highly sensitive liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) method has been developed for the simultaneous estimation of rosuvastatin and free ezetimibe. Liquid-liquid extraction was carried out using methyl-tert butyl ether after prior acidification from 300 muL human plasma. The recovery for both the analytes and their deuterated internal standards (ISs) ranged from 95.7-99.8 %. Rosuvastatin and ezetimibe were separated on Symmetry C18 column using acetonitrile and ammonium formate buffer, pH 3.5 (30:70, v/v) as the mobile phase. The analytes were well resolved with a resolution factor of 3.8. Detection and quantitation was performed under multiple reaction monitoring using ESI(+) for rosuvastatin (m/z 482.0 --> 258.1) and ESI(-) for ezetimibe (m/z 407.9 --> 271.1), respectively. A linear response function was established in the concentration range of 0.05-50.0 ng/mL and 0.01-10.0 ng/mL for rosuvastatin and ezetimibe, respectively with correlation coefficient, r(2) >/= 0.9991. The IS-normalized matrix factors for the analytes ranged from 0.963-1.023. The developed method was successfully used to compare the pharmacokinetics of fixed-dose combination tablet of rosuvastatin-ezetimibe and co-administered rosuvastatin and ezetimibe as separate tablets to 24 healthy subjects. The reliability of the assay was also assessed by reanalysis of 115 subject samples.

[6] *Melin EO, Thulesius HO, Hillman M et al.* **Abdominal obesity in type 1 diabetes associated with gender, cardiovascular risk factors and complications, and difficulties achieving treatment targets: a cross sectional study at a secondary care diabetes clinic**. BMC obesity 2018; 5:15.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29785272
ABSTRACT

Background: Abdominal obesity is linked to cardiovascular diseases in type 1 diabetes (T1D). The primary aim was to explore associations between abdominal obesity and cardiovascular complications, metabolic and inflammatory factors. The secondary aim was to explore whether achieved recommended treatment targets differed between the obese and non-obese participants. Methods: Cross sectional study of 284 T1D patients (age 18-59 years, men 56%), consecutively recruited from one secondary care specialist diabetes clinic in Sweden. Anthropometrics, blood pressure, serum-lipids and high-sensitivity C-reactive protein (hs-CRP) were collected and supplemented with data from the patients' medical records and from the Swedish National Diabetes Registry. Abdominal obesity was defined as waist circumference men/women (meters): >/=1.02/>/=0.88. Hs-CRP was divided into low-, moderate-, and high-risk groups for future cardiovascular events (< 1, 1 to 3, and > 3 to </=8.9 mg/l). Treatment targets were blood pressure </= 130/</= 80, total cholesterol </=4.5 mmol/l, LDL: </= 2.5 mmol/l, and HbA1c: </=5 2 mmol/mol (</= 6.9%). Different explanatory linear, logistic and ordinal regression models were elaborated for the associations, and calibrated and validated for goodness of fit with the data variables. Results: The prevalence of abdominal obesity was 49/284 (17%), men/women: 8%/29% (P < 0.001). Women (adjusted odds ratio (AOR) 6.5), cardiovascular complications (AOR 5.7), HbA1c > 70 mmol/mol (> 8.6%) (AOR 2.7), systolic blood pressure (per mm Hg) (AOR 1.05), and triglycerides (per mmol/l) (AOR 1.7), were associated with abdominal obesity. Sub analyses (n = 171), showed that abdominal obesity (AOR 5.3) and triglycerides (per mmol/l) (AOR 2.8) were associated with increasing risk levels of hs-CRP. Treatment targets were obtained for fewer patients with abdominal obesity for HbA1c (8% vs 21%, P = 0.044) and systolic blood pressure (51% vs 68%, P = 0.033). No patients with abdominal obesity reached all treatment targets compared to 8% in patients without abdominal obesity. Conclusions: Significant associations between abdominal obesity and gender, cardiovascular disease, and the cardiovascular risk factors low-grade inflammation, systolic blood pressure, high HbA1c, and triglycerides, were found in 284 T1D patients. Fewer patients with abdominal obesity reached the treatment targets for HbA1c and systolic blood pressure compared to the non-obese.

[7] *Ofori-Asenso R, Ilomaki J, Zomer E et al.* **A 10-Year Trend in Statin Use Among Older Adults in Australia: an Analysis Using National Pharmacy Claims Data**. Cardiovascular drugs and therapy / sponsored by the International Society of Cardiovascular Pharmacotherapy 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29790056

ABSTRACT

BACKGROUND: Statins have become standard of care in the prevention and treatment of atherosclerotic cardiovascular disease. The objective of this study was to examine the trends in statin use among Australians aged >/= 65 years for the period 2007-2016. METHODS: Data from the Pharmaceutical Benefits Scheme covering a 10% random sample of the Australian population were analysed. The 1-year prevalence and incidence of statin use were determined for each year, as were the percentage of statin dispensations according to statin type or intensity and the percentage of new users prescribed each statin type or intensity. To describe relative changes, age-sex adjusted rate ratios (RRs) and 95% confidence intervals (CIs) were determined via Poisson regression modelling using 2007 as the reference year. RESULTS: The 1-year prevalence of statin use increased consistently each year from 34.2% in 2007 to 44.1% in

2016 (RR 1.29, 95% CI 1.28-1.31). The 1-year incidence was 68.5 per 1000 in 2007 and 59.0 per 1000 in 2016 (RR 0.87, 95% CI 0.84-0.90). Women were 18% (age-adjusted rate ratio [aRR] 0.82, 95% CI 0.79-0.83) less likely than men to initiate statins across all years. The incidence of statin use was also highest among individuals aged 65-74 years, who were about 15% (sex-adjusted rate ratio [sRR] 1.15, 95% CI 1.13-1.16) and 45% (sRR 1.45, 95% CI 1.44-1.47) more likely to initiate statins than those aged 75-84 and >/= 85 years, respectively. Atorvastatin was the most commonly dispensed statin across all years. The proportion of new users dispensed high-intensity statins increased year-on-year from 23.6% in 2007 to 30.5% in 2016 (RR 1.26, 95% CI 1.21-1.31). CONCLUSION: The proportion of older adults in Australia using statins has increased over the last decade, although the incidence has declined. Atorvastatin is the most commonly dispensed statin and the use of high intensity statin has increased.

[8] *Brea A, Millan J, Ascaso JF et al.* **Fibrates in primary prevention of cardiovascular disease. Comments on the results of a systematic review of the Cochrane Collaboration**. Clinica e investigacion en arteriosclerosis : publicacion oficial de la Sociedad Espanola de Arteriosclerosis 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29789212
ABSTRACT
Fibrates are drugs that reduce triglycerides, elevate high-density lipoproteins, as well as decrease small, dense LDL particles. The results of a study have recently been published by the Cochrane Collaboration on fibrates efficacy and safety in the primary prevention of cardiovascular disease. This study includes a systematic review and a meta-analysis of 6 studies (16,135 patients) that evaluated the clinical benefits of fibrates compared to placebo use or other lipid-lowering drugs. This review showed evidence of a protective effect of the fibrates compared with placebo as regards a reduction 16% of a compound objective of death due to cardiovascular disease, non-fatal myocardial infarction, or non-fatal cerebrovascular accident (NNT: 112), and that reduce coronary morbidity and mortality by 21% (NNT: 125). In addition, fibrates could reduce previously established diabetic retinopathy. However, fibrates do not influence total mortality, or non-cardiovascular mortality. Its joint use with statins does not benefit patients without established cardiovascular disease, compared to the use of statins in monotherapy. Fibrates are safe, although they can elevate serum creatinine levels.

[9] *Masson W, Rossi E, Siniawski D et al.* **Severe hypertriglyceridemia. Clinical characteristics and therapeutic management**. Clinica e investigacion en arteriosclerosis : publicacion oficial de la Sociedad Espanola de Arteriosclerosis 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29789213
ABSTRACT
INTRODUCTION: The therapeutic management of severe hypertriglyceridaemia represents a clinical challenge. OBJECTIVES: The objectives of this study were 1) to identify the clinical characteristics of patients with severe hypertriglyceridaemia, and 2) to analyse the treatment established by the physicians in each case. METHODS: A cross-sectional study was carried out using the computerised medical records of all patients>18 years of age with a blood triglyceride level>/=1,000mg/dL between 1 January 2011 and 31 December 2016. Clinical and laboratory variables were collected. The behaviour of the physicians in the 6 months after the lipid finding

was analysed. RESULTS: A total of 420 patients were included (mean age 49.1+/-11.4 years, males 78.8%). The median of triglycerides was 1,329mg/dL (interquartile range 1,174-1,658). No secondary causes were found in 34.1% of the patients. The most frequent secondary causes were obesity (38.6%) and diabetes (28.1%). Physical activity was recommended and a nutritionist was referred to in 49.1% and 44.2% of the patients, respectively. Secondary causes were identified and attempts were made to correct them in 40.7% of cases. The most indicated pharmacological treatments were fenofibrate 200mg/day (26.5%) and gemfibrozil 900mg/day (19.3%). Few patients received the indication of omega 3 fatty acids or niacin. CONCLUSION: This study showed, for the first time in our country, the characteristics of a population with severe hypertriglyceridaemia. The therapeutic measures instituted by the physicians were insufficient. Knowing the characteristics in this particular clinical scenario could improve the current approach of these patients.

[10] *Shimizu T, Mintz GS, De Bruyne B et al.* **Relationship between left main coronary artery plaque burden and nonleft main coronary atherosclerosis: results from the PROSPECT study**. Coronary artery disease 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29781836
ABSTRACT
OBJECTIVES: Whether the severity of left main coronary artery (LMCA) disease reflects LMCA and overall coronary atherosclerotic burden is not known. We aimed to assess nonculprit LMCA disease characteristics and the relationship with atherosclerosis in the rest of the coronary arteries as well as patient outcomes. PATIENTS AND METHODS: In the PROSPECT study, 697 patients with acute coronary syndromes underwent three-vessel gray-scale and radiofrequency intravascular ultrasound after percutaneous coronary intervention. RESULTS: Overall, 552 patients with adequate LMCA imaging were compared according to LMCA plaque burden. The tertile with the highest plaque burden in the LMCA had the smallest LMCA minimum lumen area (17.4, 14.2, 10.5, lowest through highest tertiles, respectively, P<0.0001) and the greatest percent necrotic core volume (2.8, 5.6, 9.5%, lowest through highest tertiles, respectively, P<0.0001). Furthermore, the tertile with the highest plaque burden was also significantly associated with the highest overall non-LMCA percent atheroma volume within the major epicardial arteries (48.3, 49.2, 50.8%, lowest through highest tertiles, respectively, P<0.0001). After adjusting for patient background, the LMCA plaque burden was independently associated with non-LMCA percent atheroma volume (P=0.003). Of the three PROSPECT predictors of future nonculprit major adverse cardiac events (MACE) (minimum lumen area</=4 mm, plaque burden>/=70%, and virtual histology thin-cap fibroatheroma), the tertile with the highest LMCA plaque burden had the highest number of patients with at least one of three PROSPECT predictors (P=0.03). In multivariable model, though total atheroma volume (per 1%) was an independent predictor of all MACE [hazard ratio (95% confidence interval)=1.06 (1.01-1.11), P=0.02] and strong trend for non-culprit-related MACE [hazard ratio (95% confidence interval)=1.06 (1.00-1.13), P=0.06], plaque burden at LMCA was not (all MACE, P=0.90, non-culprit-related MACE, P=0.85). CONCLUSION: The severity of atherosclerosis in LMCA predicted the overall atherosclerotic plaque burden as well as the presence of high-risk plaques in the three major epicardial coronary arteries.

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[11] *Boi A, Jamthikar AD, Saba L et al.* **A Survey on Coronary Atherosclerotic Plaque Tissue Characterization in Intravascular Optical Coherence Tomography**. Current atherosclerosis reports 2018; 20:33.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29781047
ABSTRACT
PURPOSE OF REVIEW: Atherosclerotic plaque deposition within the coronary vessel wall leads to arterial stenosis and severe catastrophic events over time. Identification of these atherosclerotic plaque components is essential to pre-estimate the risk of cardiovascular disease (CVD) and stratify them as a high or low risk. The characterization and quantification of coronary plaque components are not only vital but also a challenging task which can be possible using high-resolution imaging techniques. RECENT FINDING: Atherosclerotic plaque components such as thin cap fibroatheroma (TCFA), fibrous cap, macrophage infiltration, large necrotic core, and thrombus are the microstructural plaque components that can be detected with only high-resolution imaging modalities such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT). Light-based OCT provides better visualization of plaque tissue layers of coronary vessel walls as compared to IVUS. Three dominant paradigms have been identified to characterize atherosclerotic plaque components based on optical attenuation coefficients, machine learning algorithms, and deep learning techniques. This review (condensation of 126 papers after downloading 150 articles) presents a detailed comparison among various methodologies utilized for plaque tissue characterization, classification, and arterial measurements in OCT. Furthermore, this review presents the different ways to predict and stratify the risk associated with the CVD based on plaque characterization and measurements in OCT. Moreover, this review discovers three different paradigms for plaque characterization and their pros and cons. Among all of the techniques, a combination of machine learning and deep learning techniques is a best possible solution that provides improved OCT-based risk stratification.

[12] *Toledo-Ibelles P, Mas-Oliva J*. **Antioxidants in the Fight Against Atherosclerosis: Is This a Dead End?** Current atherosclerosis reports 2018; 20:36.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29781062
ABSTRACT
PURPOSE OF REVIEW: The purpose of this review is to focus on the outcome of recent antioxidant interventions using synthetic and naturally occurring molecules established as adjuvant strategies to lipid-lowering or anti-inflammatory therapies designed to reduce the risk of cardiovascular disease. RECENT FINDINGS: To date, accumulated evidence regarding oxidation as a pro-atherogenic factor indicates that redox biochemical events involved in atherogenesis are indeed a very attractive target for the management of cardiovascular disease in the clinic. Nevertheless, although evidence indicates that redox reactions are important in the initiation and progression of atherosclerosis, oxidation with a pro-atherogenic context does not eliminate the fact that oxidation participates in many cases as an essential messenger of important cellular signaling pathways. Therefore, disease management and therapeutic goals require not only high-precision and high-sensitivity methods to detect in plasma very low amounts of reducing and oxidizing molecules but also a much better understanding of the normal processes and metabolic pathways influenced and/or controlled by oxidative stress. As

several methodologies have been specifically described for the quantification of the total antioxidant capacity and the oxidation state of diverse biological systems, a successful way to carefully study how redox reactions influence atherosclerosis can be achieved. Since there is still a lack of standardization with many of these methods, clinical trials studying antioxidant capacity have been difficult to compare and therefore difficult to use in order to reach a conclusion. We believe a comprehensive analysis of new knowledge and its relationship with the presence of plasma antioxidants and their reducing capacity will undoubtedly open new ways to understand and develop new therapeutic pathways in the fight not only against atherosclerosis but also against other degenerative diseases.

[13] *Shah P*. **Economic Evaluation of the PCSK9 Inhibitors in Prevention of the Cardiovascular Diseases**. Current cardiology reports 2018; 20:51.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29779055
ABSTRACT
PURPOSE OF REVIEW: This review aims to explore and summarize the current literature on the cardiovascular disease (CVD) healthcare burden and determine the cost-effectiveness of the PCSK9 inhibitors. RECENT FINDINGS: The CVD remain the largest cause of mortality in the USA presenting substantial healthcare cost burden reaching $555 billion in 2016 and projected to rise to $1.1 trillion by 2035. The PCSK9 inhibitors have shown strong efficacy in LDLC lowering, but its price of ~ 14,000-14,600 per patient per year coupled with ~ 2.2-2.8 years of cardiovascular outcome data has created many controversies surrounding its cost-effectiveness. To determine the cost-effectiveness of the PCSK9 inhibitors, various simulation models and risk-based stratification and case-by-case patient approachs have yielded divisive data which need to be reassessed as per the ODYSSEY and long-term CVD outcomes. Further studies are warranted to evaluate the long-term CVD event rates of patients on the PCSK9 inhibitors to determine its true cost-effectiveness.

[14] *Kawasaki R, Konta T, Nishida K*. **Lipid-lowering medication use is associated with decreased risk of diabetic retinopathy and its treatments in patients with type 2 diabetes: a real-world observational analysis of a health claims database**. Diabetes Obes Metab 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29790265
ABSTRACT
AIMS: Fenofibrate and statins reduced the risk of diabetic retinopathy (DR) related treatment in clinical trials. We aimed to determine whether lipid-lowering medication use reduce the risk of DR and its treatments in patients with type 2 diabetes using a real-world health claims database. METHODS: This was an observational analysis using a nation-wide health claims database of the Japan Medical Data Center (JMDC). Type 2 diabetes was defined by the ICD-10 codes with glucose-lowering medication use. Lipid-lowering medication use at least one year was confirmed by the Anatomical Therapeutic Chemical Classification System. DR and diabetic macular edema (DME) were determined by ICD-10; DR related treatments were determined by health insurance claims. A propensity score for lipid-lowering medication use was estimated, and a doubly robust estimator using the inverse probability weighting model with regression adjustment was obtained to estimate odds ratios (OR) with 95% confidence interval (95%CI) for cumulative incidence of DR and its treatments over 3 years. RESULTS: There were 69,070

persons with type 2 diabetes at baseline. DR developed in 5,687 persons over 3 years. Lipid-lowering medication use was associated with decreased risk of incidence of DR (OR 0.772, 95%CI 0.720-0.827; p<0.001). Lipid-lowering medication use was also associated with decreased incidence of DME, any treatments for DR, laser photocoagulation, and vitrectomy in patients with DR at baseline. CONCLUSIONS: In a population of patients with type 2 diabetes with a variety of risk profile, lipid-lowering medication use reduced the risk of DR and its treatments of laser photocoagulation and vitrectomy.

[15] *Rodriguez-Cuenca S, Carobbio S, Barcelo-Coblijn G et al.* **P465L ppargamma mutation confers partial resistance to the hypolipidemic action of fibrates**. Diabetes Obes Metab 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29790245
ABSTRACT
Familial partial lipodystrophic syndrome 3 (FPLD3) is associated with mutations in the transcription factor PPARgamma. One of these mutations, the P467L, confers a dominant negative effect. We and others have previously investigated the pathophysiology associated to this mutation using a humanised mouse model that recapitulates most of the clinical symptoms observed in patients when phenotyped under different experimental conditions. One of the key clinical manifestations observed both, in humans and mouse models, is the ectopic accumulation of fat in the liver. Here, we dissect the molecular mechanisms that contribute to the excessive accumulation of lipids in the liver and characterise the negative effect of this PPARgamma mutation on the activity of PPARalpha in vivo when activated by fibrates. P465L mice have increased levels of insulin and free fatty acids (FFA), exhibit decreased levels of Very Low Density Lipoproteins (VLDL) when fed high fat diet (HFD) and a partial impaired response to the hypolipidemic action of WY14643. This indicates that the deleterious effects of P465L-PPARgamma mutation may be magnified by their collateral negative effect on PPARalpha function. This article is protected by copyright. All rights reserved.

[16] *Ginsberg HN, Farnier M, Robinson JG et al.* **Efficacy and Safety of Alirocumab in Individuals with Diabetes Mellitus: Pooled Analyses from Five Placebo-Controlled Phase 3 Studies**. Diabetes Ther 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29779195
ABSTRACT
INTRODUCTION: Diabetes mellitus (DM) carries an elevated risk for cardiovascular disease. Here, we assessed alirocumab efficacy and safety in people with/without DM from five placebo-controlled phase 3 studies. METHODS: Data from up to 78 weeks were analyzed in individuals on maximally tolerated background statin. In three studies, alirocumab 75 mg every 2 weeks (Q2W) was increased to 150 mg Q2W at week 12 if week 8 low-density lipoprotein cholesterol (LDL-C) was >/= 70 mg/dL; two studies used alirocumab 150 mg Q2W throughout. The primary endpoint was percentage change in LDL-C from baseline to week 24. RESULTS: In the alirocumab 150 mg pool (n = 2416), baseline LDL-C levels were 117.4 mg/dL (DM) and 130.6 mg/dL (without DM), and in the 75/150 mg pool (n = 1043) 112.8 mg/dL (DM) and 133.0 mg/dL (without DM). In the 150 mg Q2W group, week 24 LDL-C reductions from baseline were observed in persons with DM (- 59.9%; placebo, - 1.4%) and without DM (- 60.6%; placebo, +

1.5%); 77.7% (DM) and 76.8% (without DM) of subjects achieved LDL-C < 70 mg/dL. In the alirocumab 75/150 mg group, 26% (DM) and 36% (without DM) of subjects received dose increase. In this group, week 24 LDL-C levels changed from baseline by - 43.8% (DM; placebo, + 0.3%) and - 49.7% (without DM; placebo, + 5.1%); LDL-C < 70 mg/dL was achieved by 68.3% and 65.8% of individuals, respectively. At week 24, alirocumab was also associated with improved levels of other lipids. Adverse event rates were generally comparable in all groups (79.8-82.0%). CONCLUSIONS: Regardless of DM status, alirocumab significantly reduced LDL-C levels; safety was generally similar. FUNDING: Sanofi and Regeneron Pharmaceuticals, Inc. Plain language summary available for this article.

[17] *Jenkins DJA, Kendall CWC, Lamarche B et al.* **Nuts as a replacement for carbohydrates in the diabetic diet: a reanalysis of a randomised controlled trial**. Diabetologia 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29789878

ABSTRACT

AIMS/HYPOTHESIS: In line with current advice, we assessed the effect of replacing carbohydrate consumption with mixed nut consumption, as a source of unsaturated fat, on cardiovascular risk factors and HbA1c in type 2 diabetes. The data presented here are from a paper that was retracted at the authors' request (https://doi.org/10.2337/dc16-rt02) owing to lack of adjustment for repeated measures in the same individual. Our aim, therefore, was to fix the error and add new complementary data of interest, including information on clotting factors and LDL particle size. METHODS: A total of 117 men and postmenopausal women with type 2 diabetes who were taking oral glucose-lowering agents and with HbA1c between 47.5 and 63.9 mmol/mol (6.5-8.0%) were randomised after stratification by sex and baseline HbA1c in a parallel design to one of three diets for 3 months: (1) 'full-dose nut diet' (n = 40): a diet with 2.0 MJ (477 kcal) per 8.4 MJ (2000 kcal) energy provided as mixed nuts (75 g/day); (2) 'full-dose muffin diet' (n = 39): a diet with 1.97 MJ (471 kcal) per 8.4 MJ (2000 kcal) energy provided as three whole-wheat muffins (188 g/day), with a similar protein content to the nuts, and the same carbohydrate-derived energy content as the monounsaturated fatty acid-derived energy content in the nuts; or (3) 'half-dose nut diet' (n = 38): a diet with 1.98 MJ (474 kcal) per 8.4 MJ (2000 kcal) energy provided as half portions of both the nuts and muffins. The primary outcome was change in HbA1c. The study was carried out in a hospital clinical research centre and concluded in 2008. Only the statistician, study physicians and analytical technicians could be blinded to the group assessment. RESULTS: A total of 108 participants had post-intervention data available for analysis (full-dose nut group, n = 40; full-dose muffin group, n = 35; half-dose nut group, n = 33). Compared with the full-dose muffin diet, the full-dose nut diet provided 9.2% (95% CI 7.1, 11.3) greater total energy intake from monounsaturated fat. The full-dose nut diet (median intake, 75 g/day) also reduced HbA1c compared with the full-dose muffin diet by -2.0 mmol/mol (95% CI -3.8, -0.3 mmol/mol) (-0.19% [95% CI -0.35%, -0.02%]), (p = 0.026). Estimated cholesterol levels in LDL particles with a diameter <255 angstrom [LDL-c<255A]) and apolipoprotein B were also significantly decreased after the full-dose nut diet compared with the full-dose muffin diet. According to the dose response, the full-dose nut diet is predicted to reduce HbA1c (-2.0 mmol/mol [-0.18%]; p = 0.044), cholesterol (-0.25 mmol/l; p = 0.022), LDL-cholesterol (-0.23 mmol/l; p = 0.019), non-HDL-cholesterol (-0.26 mmol/l; p = 0.020), apolipoprotein B (-0.06 g/l, p = 0.013) and LDL-c<255A (-0.42 mmol/l; p < 0.001). No serious

study-related adverse events occurred, but one participant on the half-dose nut diet was hospitalised for atrial fibrillation after shovelling snow. CONCLUSIONS/INTERPRETATION: Nut intake as a replacement for carbohydrate consumption improves glycaemic control and lipid risk factors in individuals with type 2 diabetes. TRIAL REGISTRATION: ClinicalTrials.gov NCT00410722 FUNDING: The study was funded by the International Tree Nut Council Nutrition Research and Education Foundation, the Peanut Institute, Loblaw Companies and the Canada Research Chairs Program of the Government of Canada.

[18] *Oh M, Ghim JL, Park SE et al.* **Pharmacokinetic comparison of a fixed-dose combination versus concomitant administration of fimasartan, amlodipine, and rosuvastatin using partial replicated design in healthy adult subjects**. Drug design, development and therapy 2018; 12:1157-1164.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29780236
ABSTRACT
Objective: The aim of this study was to compare the pharmacokinetics (PK) and safety profiles of a fixed-dose combination (FDC) formulation of fimasartan, amlodipine, and rosuvastatin with the co-administration of the two products by using a replicated crossover study design in healthy male subjects. Results: This was an open-label, randomized, three-sequence, three-period replicated crossover study in healthy male subjects. The replicated crossover design was done because of high coefficient of variation of PK parameter for fimasartan, that is, >30%. With a 14 days washout period, an FDC tablet containing 60 mg fimasartan, 10 mg amlodipine, and 20 mg rosuvastatin was administered only once, and separate formulations of fimasartan/amlodipine 60 mg/10 mg FDC tablet and 20 mg rosuvastatin tablet administered twice. Blood samples were collected up to 72 hours following drug administration. The plasma concentrations of fimasartan, amlodipine, and rosuvastatin were measured by liquid chromatography tandem mass spectrometry. Safety was assessed by evaluating vital signs, clinical laboratory parameters, physical examinations, and medical interviews. Results: The geometric mean ratios and 90% confidence intervals (CIs) for the maximum plasma concentration (Cmax) and area under the curve from time zero to the last measurable sampling time (AUCt) were 1.0776 (0.9201-1.2622) and 0.9978 (0.9538-1.0439) for fimasartan, 1.0038 (0.9782-1.0301) and 1.0055 (0.9828-1.0288) for amlodipine, and 1.0006 (0.9290-1.0776) and 0.9986 (0.9532-1.0461) for rosuvastatin, respectively. A total of 22 adverse events (AEs) were reported by 60 subjects; there were no significant differences in the incidence of AEs between the two groups. Conclusion: The 90% CI of the Cmax of fimasartan was within the widened acceptance limit, ln(0.6984)-ln(1.4319). The 90% CIs of the other PK parameters for drugs were between ln(0.8) and ln(1.25). These results suggest that the FDC formulation is pharmacokinetically bioequivalent and has a similar safety profile, to the co-administration of its three constituent drugs.

[19] *Buonuomo PS, Macchiaiolo M, Leone G et al.* **Treatment of homozygous familial hypercholesterolaemia in paediatric patients: A monocentric experience**. European journal of preventive cardiology 2018:2047487318776836.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29785886
ABSTRACT

Literature update week 21 (2018)

Background Homozygous familial hypercholesterolaemia is a rare life-threatening disease characterized by markedly elevated low-density lipoprotein cholesterol (LDL-C) concentrations and accelerated atherosclerosis. The presence of double gene defects in the LDL-Receptor, either the same defect (homozygous) or two different LDL-raising mutations (compound heterozygotes) or other variants, identify the homozygous phenotype (HopFH). Apheresis is a procedure in which plasma is separated from red blood cells before the physical removal of LDL-C or the LDL-C is directly removed from whole blood. It is currently the treatment of choice for patients with HopFH whose LDL-C levels are not able to be reduced to target levels with conventional lipid-lowering drug therapy. Design The aim of this study is to report a cohort of six paediatric patients and to evaluate the long term efficacy of combined medical therapy and LDL-apheresis on LDL-C reduction. Methods We collected data from six children with confirmed diagnosis of HopFH (two females and four males; age range at diagnosis 3-8 years, mean 6 +/- 1 years) from a single clinical hospital in Italy from 2007 to 2017. Results Clinical manifestations and outcomes may greatly vary in children with HopFH. Medical therapy and LDL-apheresis for the severe form should be started promptly in order to prevent cardiovascular disease. Conclusions Lipoprotein apheresis is a very important tool in managing patients with HopFH at high risk of cardiovascular disease. Based on our experience and the literature data, the method is feasible in very young children, efficient regarding biological results and cardiac events, and safe with minor side-effects and technical problems. We advise treating homozygous and compound heterozygous children as soon as possible.

[20] *Veraldi GF, Nocini PF, Eccher A et al.* **Correlation between MDCTA and Carotid Plaque Histological Heterogeneity: A Pilot Study**. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29784555

ABSTRACT

BACKGROUND: The aim of this pilot study was to identify multidetector computed tomography angiography (MDCTA) features that may help identify carotid atherosclerotic plaques (CAPs) with severe histological heterogeneity. METHODS: Thirty-one CAPs (9 symptomatic) were evaluated histologically using a semiquantitative scale. The CAPs were assessed for the presence of ulceration, lipids, fibrosis, thrombotic deposits, haemorrhage, neovascularisation, and inflammation. A CAP presenting at least five of these histological features was defined as a severe heterogeneous plaque (Group A); in all other cases it was defined as a mild to moderate heterogeneous plaque (Group B). The non-calcified plaque tissue was segmented in pre-operative MDCTA. Median and mean intensity and percentages of soft tissue voxels with a value smaller than or equal to certain thresholds (from 20 HU to 200 HU with a constant distance of 20 HU) were calculated. Comparison of intensity measurements was analysed by Mann-Whitney U test and receiver operating characteristic (ROC) analysis. In order to assess the method reliability, values showing better performance were compared using the Wilcoxon signed rank test and k-Cohen test according to ROC analysis. RESULTS: According to histological analysis 18 CAPs were classified as belonging to Group B and 13 to Group A. The percentages of soft tissue with density </= 40 (TH_40), 60 (TH_60), 80 (TH_80), and 100 HU (TH_100) were statistically significantly greater in plaques of Group A (respectively p = .016, p = .002, p = .001, p = .007). The mean (p = .025) and median (p = .014) intensity were statistically significantly

lower in the plaques of Group A. TH_60 and TH_80 showed the greatest accuracy (0.81) with similar performance in term of AUC and sensitivity/specificity (TH_60: 0.82, 0.62, 0.94; TH_80: 0.83, 0.69, 0.89, respectively, for AUC, sensitivity and specificity). Reliability analysis showed good repeatability and reproducibility of these measurements. CONCLUSIONS: The findings have demonstrated lower density of the non-calcified tissue in the plaques of Group A with higher TH_60 and TH_80 soft tissue percentages with respect to CAPs of Group B.

[21] *Encina C, Marquez-Ruiz G, Holgado F et al.* **Effect of spray-drying with organic solvents on the encapsulation, release and stability of fish oil**. Food chemistry 2018; 263:283-291.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29784318
ABSTRACT
Fish-oil (FO) was encapsulated with hydroxypropylcelullose (HPC) by conventional spray-drying with water (FO-water) and solvent spray-drying with ethanol (FO-EtOH), methanol (FO-MeOH) and acetone (FO-Acet) in order to study the effect of the solvent on the encapsulation efficiency (EE), microparticle properties and stability of FO during storage at 40 degrees C. Results showed that FO-Acet presented the highest EE of FO (92.0%), followed by FO-EtOH (80.4%), FO-MeOH (75.0%) and FO-water (71.1%). A decrease of the dielectric constant increased the EE of FO, promoting triglyceride-polymer interactions instead of oil-in-water emulsion retention. FO release profile in aqueous model was similar for all FO-microparticles, releasing only the surface FO, according to Higuchi model. Oxidative stability of FO significantly improved by spray-drying with MeOH, both in surface and encapsulated oil fractions. In conclusion, encapsulation of FO by solvent spray-drying can be proposed as an alternative technology for encapsulation of hydrophobic molecules.

[22] *Leite GAA, Figueiredo TM, Guerra MT et al.* **Ascorbic acid co-administered with rosuvastatin reduces reproductive impairment in the male offspring from male rats exposed to the statin at pre-puberty**. Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29778496
ABSTRACT
Obesity during childhood and adolescence is closely related to dysfunctions on lipid profile in children. Rosuvastatin is a statin that decreases serum total cholesterol. Ascorbic acid is an important antioxidant compound for male reproduction. Pre-pubertal male rats were distributed into six experimental groups that received saline solution 0.9% (vehicle), 3 or 10mg/kg/day of rosuvastatin, 150mg/day of ascorbic acid, or 3 or 10mg/kg/day of rosuvastatin co-administered with 150mg/day of ascorbic acid by gavage from post-natal day (PND)23 until PND53. Rats were maintained until adulthood and mated with nulliparous females to obtain the male offspring, whose animals were evaluated at adulthood in relation to reproductive parameters. This study is a follow up of a previous paper addressing potential effects on F0 generation only (Leite et al., 2017). Male offspring from rosuvastatin-exposed groups showed increased sperm DNA fragmentation, androgen depletion and impairment on the testicular and epididymal structure. Ascorbic acid coadministered to the fathers ameliorated the reproductive damage in the offspring. In summary, paternal exposure to rosuvastatin may affect the reproduction in the male offspring; however, paternal supplementation with ascorbic acid was

able to reduce the reproductive impairment in the male offspring caused by statin treatment to the fathers.

[23] *Song J, Hu M, Li C et al.* **Dose-dependent effects of fish oil on cardio-metabolic biomarkers in healthy middle-aged and elderly Chinese people: a double-blind randomized controlled trial**. Food & function 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29781483
ABSTRACT
n-3PUFA consumption has been widely accepted as a nutritional strategy for the secondary prevention of cardiovascular events in patients at high risk of cardiovascular disease (CVD), but little is known about the dose-response relationship between dietary n-3PUFA and serum biomarkers associated with cardiovascular health in the general population. The present study involved a 12-week double-blind, randomized controlled trial to explore the effects of fish oil with different doses (0.31, 0.62 and 1.24 g d-1 of EPA and DHA) on serum fatty acids and cardio-metabolic biomarkers including adiponectin, inflammatory markers, lipid profiles and fasting glucose in healthy middle-aged and elderly Chinese people. 240 volunteers met our inclusion criteria. A total of 39 subjects dropped out and 201 finally completed the intervention. No significant differences in baseline characteristics and daily intakes of dietary nutrients were detected among all groups. After a 12-week intervention, fish oil dose-dependently enhanced serum EPA, DHA, n-3PUFA and adiponectin (except for 0.31 g d-1), but decreased serum n-6/n-3PUFA, TG and fasting glucose. Changes in the above indicators from the baseline to week 12 in fish oil groups significantly differed from those in the control. Meanwhile, all the doses of EPA and DHA led to decreases in serum CRP; only 1.24 g d-1 led to an increase in HDL-C with a concurrent decrease in TC/HDL-C even though these changes were not significantly different among all groups. All the findings suggested that fish oil dose-dependently regulated serum PUFA and cardio-metabolic biomarkers including adiponectin, CRP, lipid profiles and fasting glucose in healthy middle-aged and elderly Chinese people who consumed insufficient dietary n-3PUFA, and the most desirable changes were observed for 1.24 g d-1.

[24] *Yamashita S, Masuda D, Arai H, Matsuzawa Y*. **Cultural Barriers in the Treatment of Dyslipidemia: A Survey of Japanese Physician Attitudes**. Journal of atherosclerosis and thrombosis 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29780067
ABSTRACT
AIMS: To gain a more accurate understanding of the current real-world management of dyslipidemia in Japan, an online survey was conducted in a variety of physicians from five medical fields. METHODS: A web-based survey with online questionnaire was designed, and members of an on-line information service for physicians were invited to participate. The survey enrolled 500 physicians, 100 in each of five categories: cardiology; diabetes, metabolism and endocrinology; neurology/neurosurgery/stroke medicine; general internal medicine (hospitals >/=20 beds), and general internal medicine (self-employed practitioners at clinics or small hospitals </=19 beds). RESULTS: Regardless of their specialties, most physicians recognized high low density lipoprotein cholesterol level as an important risk for atherosclerotic cardiovascular disease. Physicians with expertise in cardiology, diabetes, metabolism and

endocrinology were most in favor of drug-based cholesterol lowering. Specialists in neurology/neurosurgery/stroke medicine and in general internal medicine were more concerned about statin safety and aggressive lipid-lowering therapy than those in cardiology and diabetes, metabolism and endocrinology, and tended to treat fewer patients with familial hypercholesterolemia (FH). Especially, those in general internal medicine (self-employed practitioners at clinics or small hospitals </=19 beds) made less use of techniques for diagnosing FH. CONCLUSIONS: Awareness of target values for lipid management and of adverse reactions to drug therapy appears to vary somewhat depending on the participant's medical specialty. We also found that FH is probably underdiagnosed in Japan today. Further educations on proper diagnosis and management of dyslipidemia are required for physicians who are not specialized in cardiovascular health.

[25] *Aljenedil S, Ruel I, Watters K, Genest J*. **Severe xanthomatosis in heterozygous familial hypercholesterolemia**. Journal of clinical lipidology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29778561

ABSTRACT

BACKGROUND: Familial hypercholesterolemia is a genetic lipoprotein disorder characterized by elevated plasma low-density lipoprotein cholesterol level, (tendinous xanthomas, xanthelasmas, and premature arcus corneus) and early onset atherosclerotic cardiovascular disease. Familial hypercholesterolemia is caused by mutations in the low-density lipoprotein receptor, apolipoprotein B or proprotein convertase subtilisin/kexin type 9 genes. Rare mutations in low-density lipoprotein receptor adapter protein 1, APOE p.Leu167del or lysosomal acid lipase genes can mimic FH. The prevalence of heterozygous familial hypercholesterolemia is estimated to be 1/250 worldwide, although some populations with founder effects show a higher prevalence. The rare homozygous form has an estimated prevalence of 0.000004 or 1/250,000 and is characterized by markedly elevated low-density lipoprotein cholesterol, skin manifestations (planar xanthomas, tendinous xanthomas) in childhood and extremely premature atherosclerotic cardiovascular disease. While tendinous xanthomas are considered pathognomonic for familial hypercholesterolemia, they can also be found in rare diseases, including sitosterolemia. Here, we report a case of severe tendinous xanthomatosis with heterozygous familial hypercholesterolemia due to the low-density lipoprotein receptor del >15 kb mutation. The phenotypic expression of the disease is out of proportion with the genetic diagnosis or biochemical measurements. CASE REPORT: We report the case of 51-year-old woman of French-Canadian origin diagnosed with heterozygous familial hypercholesterolemia since age 12. She presented with hypercholesterolemia with total cholesterol 7.6 mmol/L, with an imputed low-density lipoprotein cholesterol level of 6.5 mmol/L. She had extensive tendinous xanthomas of the Achilles tendons, knees, elbows and metacarpophalangeal joints. Because of cosmetic disfigurement, she had multiple excisions of Achilles, knee and elbow xanthomas, albeit with rapid recurrence. Our patient has a significant family history of lung cancer and other autoimmune diseases associated with familial hypercholesterolemia and xanthoma. Lipid-lowering therapy was started, at age 12; which included initially cholestyramine, then changed to statin and ezetimibe. Eventually, evolocumab was added. Despite trying different lipid-lowering therapy, there has been no noticeable decrease in the size of the xanthomas. CONCLUSION: Our patient has severe xanthomatosis out

of proportion with the genetic diagnosis or biochemical measurements. Her xanthomatosis did not improve by pharmacological therapy consisting of statins and evolocumab despite a 50% reduction in low-density lipoprotein cholesterol. It is likely that the patient presented here has a second genetic disorder that leads to extensive xanthomatosis.

[26] *Barter PJ, Waters DD*. **Variations in time to benefit among clinical trials of cholesterol-lowering drugs**. Journal of clinical lipidology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29779997
ABSTRACT
BACKGROUND: Time to benefit (TTB) in clinical trials of cholesterol-lowering drugs is important because it may provide a clue as to the potential mechanism of action of the drug, it is helpful in determining when to stop a trial for futility, and it may inform treatment decisions in subjects with reduced life expectancy. OBJECTIVE: To compare TTB among clinical trials of cholesterol-lowering drugs. METHODS: We examined TTB in 24 trials of cholesterol-lowering drugs with positive outcomes. Benefit curves were constructed by subtracting the curve for a placebo or comparator drug from the curve for active treatment. RESULTS: TTB ranged from 1 to 30 (mean 13.1) months, being shorter in trials of statins (n = 17) compared to nonstatins (n = 7), 10.3 vs 20.0 months. Among statin trials, TTB was shorter with atorvastatin (n = 6) than in trials with other statins (n = 11), 4.75 compared to 11.4 months. CONCLUSIONS: TTB is variable among trials of cholesterol-lowering drugs, being shorter with statin compared to nonstatin drugs. TTB is shorter with atorvastatin than with other statins. For trials of new cholesterol-lowering drugs, outcome curves that do not separate for up to 30 months do not preclude eventual benefit.

[27] *Dalugama C, Pathirage M, Kularatne SAM*. **Delayed presentation of severe rhabdomyolysis leading to acute kidney injury following atorvastatin-gemfibrozil combination therapy: a case report**. Journal of medical case reports 2018; 12:143.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29784023
ABSTRACT
BACKGROUND: Rhabdomyolysis is a rare but serious complication of lipid-lowering therapy. Statin and fibrate combination increases the risk of rhabdomyolysis possibly by pharmacodynamic interactions. Advanced age, diabetes, hypothyroidism, polypharmacy, and renal impairment are known to increase the risk of rhabdomyolysis. Management strategies include fluid resuscitation and urine alkalinization. Renal indications such as refractory hyperkalemia, acidosis, fluid overload, or uremic complications mandate renal replacement therapy in rhabdomyolysis. CASE PRESENTATION: We report the case of a 62-year-old Sri Lankan Sinhalese man with dyslipidemia, type 2 diabetes mellitus with renal impairment, and hypothyroidism who was on atorvastatin; he was started on gemfibrozil and developed muscle symptoms. Although gemfibrozil was discontinued soon after, he presented with rhabdomyolysis with acute kidney injury 1 month later. He needed hemodialysis due to refractory hyperkalemia, metabolic acidosis, and fluid overload. CONCLUSIONS: Rhabdomyolysis is a rare but serious complication due to lipid-lowering therapy with statins and fibrates. Treating physicians should be aware and patients should be warned to report about muscle symptoms after starting statins or fibrates. Rhabdomyolysis may occur with mild symptoms and signs and may occur later, even after discontinuation of the drug.

[28] *Kim U, Leipsic JA, Sellers SL et al.* **Natural History of Diabetic Coronary Atherosclerosis by Quantitative Measurement of Serial Coronary Computed Tomographic Angiography: Results of the PARADIGM Study (Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography Imaging)**. JACC. Cardiovascular imaging 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29778853
ABSTRACT
OBJECTIVES: This study aimed to determine the rate and extent of plaque progression (PP), changes in plaque features, and clinical predictors of PP in patients with diabetes mellitus (DM). BACKGROUND: The natural history of coronary PP in patients with DM is not well established. METHODS: A total of 1,602 patients (age 61.3 +/- 9.0 years; 60.3% men; median scan interval 3.8 years) who underwent serial coronary computed tomography angiography over a period of at least 24 months were enrolled and analyzed from the PARADIGM (Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography Imaging) trial. Study endpoints were changes in plaque features in diabetics with PP and risk factors for PP by serial coronary computed tomography angiography between patients with and without DM. PP was defined if plaque volume at follow-up minus plaque volume at baseline was >0. RESULTS: DM was an independent risk factor for PP (84.6%; 276 of 326 patients with PP) in multivariate analysis (odds ratio [OR]: 1.526; 95% confidence interval [CI]: 1.100 to 2.118; p = 0.011). Independent risk factors for PP in patients with DM were male sex (OR: 1.485; 95% CI: 1.003 to 2.199; p = 0.048) and mean plaque burden at baseline >/=75% (OR: 3.121; 95% CI: 1.701 to 5.725; p </= 0.001). After propensity matching, percent changes in overall plaque volume (30.3 +/- 36.9% in patients without DM and 36.0 +/- 29.7% in those with DM; p = 0.032) and necrotic core volume (-7.0 +/- 35.8% in patients without DM and 21.5 +/- 90.5% in those with DM; p = 0.007) were significantly greater in those with DM. The frequency of spotty calcification, positive remodeling, and burden of low-attenuation plaque were significantly greater in patients with DM. CONCLUSIONS: People with DM experience greater PP, particularly significantly greater progression in adverse plaque, than those without DM. Male sex and mean plaque burden >75% at baseline were identified as independent risk factors for PP.

[29] *Ageev FT, Blankova ZN, Samsonova NS*. **[The effect of changing of conventional antihypertensive therapy to a triple fixed combination therapy with rosuvastatin in high cardiovascular risk patients]**. Kardiologiia 2018:46-54.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29782289
ABSTRACT
BACKGROUND: The low efficiency of recommended therapy for reducing cardiovascular risk (CV) in patients with arterial hypertension even with an effective blood pressure decrease is often due to the persistence of high blood cholesterol and arterial stiffness. Among the effective ways to achieve the goal of therapy is considered the changing to a single-pill combinations (SPCs) of two antihypertensive drugs and statin. AIM: To assess influence of fixed combination consisted of amlodipine, lisinopril and rosuvastatin to the dynamic of lipid spectrum, blood pressure level and elastic properties of arteries in patients with arterial hypertension and high risk of cardio-vascular complications being transferred from their preceding antihypertensive therapy. MATERIALS AND METHODS: 113 patients with

atherosclerosis of brachiocephalic arteries (BCA) receiving antihypertensive and partially taking statins therapy were assessed cholesterol, low-density lipoprotein cholesterol (LDL-C), peripheral and central blood pressure, carotid-femoral pulse wave velocity (PWV) initially and after 12 months of taking amlodipine + lisinopril + rosuvastatin (A+L+R) SPCs. RESULTS: The administration of A+L+R SPCs for 12 months was associated with an increasing of number of patients with the achieved target blood pressure.

[30] *Mafham M, Haynes R*. **PCSK9 inhibition: ready for prime time in CKD?** Kidney international 2018; 93:1267-1269.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29792269
ABSTRACT
Lowering LDL cholesterol reduces the risk of atherosclerotic vascular disease in a wide range of patients with chronic kidney disease, with no evidence of a threshold below which further reductions no longer reduce risk. Statins safely lower LDL cholesterol, but novel inhibitors of proprotein convertase subtilisin kexin 9 (PCSK9) provide additional reductions which may reduce atherosclerotic vascular disease yet further in this high risk population.

[31] *Kim BJ, Lee EJ, Kwon SU et al.* **Prevention of cardiovascular events in Asian patients with ischaemic stroke at high risk of cerebral haemorrhage (PICASSO): a multicentre, randomised controlled trial**. Lancet neurology 2018; 17:509-518.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29778364
ABSTRACT
BACKGROUND: The optimal treatment for patients with ischaemic stroke with a high risk of cerebral haemorrhage is unclear. We assessed the efficacy and safety of cilostazol versus aspirin, with and without probucol, in these patients. METHODS: In this randomised, controlled, 2 x 2 factorial trial, we enrolled patients with ischaemic stroke with a history of or imaging findings of intracerebral haemorrhage or two or more microbleeds from 67 centres in three Asian countries. Patients were randomly assigned (1:1:1:1) to receive oral cilostazol (100 mg twice a day), aspirin (100 mg once a day), cilostazol plus probucol (250 mg twice a day), or aspirin plus probucol with centralised blocks stratified by centre. Cilostazol versus aspirin was investigated double-blinded; probucol treatment was open-label, but the outcome assessor was masked to assignment. The co-primary outcomes were incidence of the composite of stroke, myocardial infarction, or vascular death (efficacy) and incidence of haemorrhagic stroke (safety), which were assessed in intention-to-treat and modified intention-to-treat populations. Efficacy was analysed with a non-inferiority test and a superiority test if non-inferiority was satisfied. Safety was assessed with a superiority test only. This trial is registered with ClinicalTrials.gov, NCT01013532. FINDINGS: Between Aug 1, 2009, and Aug 31, 2015, we randomly assigned 1534 patients to one of the four study groups, of whom 1512 were assessed for the co-primary endpoints. During a median follow-up of 1.9 years (IQR 1.0-3.0), the incidence of composite vascular events was 4.27 per 100 person-years in patients who received cilostazol and 5.33 per 100 person-years in patients who received aspirin (HR 0.80, 95% CI 0.57-1.11; non-inferiority p=0.0077; superiority p=0.18). Incidence of cerebral haemorrhage was 0.61 per 100 person-years in patients who received cilostazol and 1.20 per 100 person-years in those who received aspirin (HR 0.51, 97.5% CI 0.20-1.27; superiority p=0.18). The incidence of

vascular events was 3.91 per 100 person-years in the probucol group compared with 5.75 per 100 person-years in the non-probucol group (HR 0.69, 95% CI 0.50-0.97; superiority p=0.0316). The incidence of cerebral haemorrhage was 0.72 per 100 person-years in the probucol group and 1.11 per 100 person-years in the non-probucol group (HR 0.65, 97.5% CI 0.27-1.57; p=0.55). Adverse events were similar across the four study groups; the most common events were dizziness, headache, diarrhoea, and constipation. INTERPRETATION: In patients with ischaemic stroke at high risk of cerebral haemorrhage, cilostazol was non-inferior to aspirin for the prevention of cardiovascular events, but did not reduce the risk of haemorrhagic stroke. Addition of probucol to aspirin or cilostazol could be beneficial for reducing the incidence of cardiovascular events. FUNDING: Korea Otsuka Pharmaceutical.

[32] *Liu Y, Rong Z, Xiang D et al.* **Detection technologies and metabolic profiling of bile acids: a comprehensive review**. Lipids in health and disease 2018; 17:121.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29792192
ABSTRACT
Bile acids (BAs) are important regulatory factors of life activities, which are involved in the regulation of glucose, lipid and energy metabolisms, and closely associated with intestinal hormones, microbiotas and energy balance. BAs abnormalities easily lead to inflammation and metabolic diseases, in turn, the progress of diseases could influence characteristics of BAs. Therefore, accurate detection of BAs contents is of great significance to disease prevention, diagnosis and treatment. At present, the most widely used enzymatic method in clinical practice is applicable to the detection of total bile acid (TBA). In laboratory research, different types of BAs can be accurately separated and quantified by liquid chromatography-mass spectrometry (LC-MS). The metabolic profiling of BAs based on detection technologies can completely and accurately monitor their types and contents, playing a crucial role in disease prevention, diagnosis and treatment. We herein reviewed the main detection technologies of BAs and the application of metabolic profiling in related diseases in recent years.

[33] *Reklou A, Doumas M, Imprialos K et al.* **Reduction of Vascular Inflammation, LDL-C, or Both for the Protection from Cardiovascular Events?** The open cardiovascular medicine journal 2018; 12:29-40.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29785212
ABSTRACT
Background: Low density lipoprotein cholesterol (LDL-C) and low grade arterial inflammation are key pathogenic factors for atherosclerosis and its manifestation, cardiovascular disease (CVD). Objective: In this narrative review we assessed if decreasing LDL-C levels or inflammation or both is more effective in reducing CVD events. Results: In the Scandinavian Simvastatin Survival Study (4S), all statin trials of the 90s' and the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) the benefit came from the LDL-C reduction. In the GREak and Atorvastatin Coronary heart disease Evaluation (GREACE), the Treating to New Targets (TNT), and the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trials both mechanisms in combination produced significant benefits. In the Atorvastatin for Reduction of MYocardial Damage during Angioplasty (ARMYDA) trials and the Canakinumab Antiinflammatory

Thrombosis Outcome Study (CANTOS) with a human antibody targeting IL-1beta with no lipid lowering effect, the reduction in arterial inflammation played the only beneficial role because there was no change in lipids levels. Conclusion: Both LDL-C and inflammation reduction are beneficial to the reduction of CVD risk. However, canakinumab is a very expensive drug that only induced a 15% reduction in CVD events, thus drastically reducing the possibility for it to be used in clinical practice. Besides, canakinumab is associated with increased infections, some fatal. A potent statin with anti-inflammatory effects is probably the best choice for the majority of those needing hypolipidaemic drug therapy.

[34] *Molokhia M, Bhatia S, Nitsch D*. **Genetic determinants of statin-associated myopathy**. Personalized medicine 2008; 5:481-494.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29783452
ABSTRACT
Lipid-lowering drugs, especially 3-hydroxy-3-methylglutaryl coenzyme A inhibitors (statins), are widely used in the treatment of patients with increased risk of cardiovascular disease, with well-documented benefits. However, in rare cases, lipid-lowering drugs may cause myopathy or rhabdomyolysis, the risk of which is increased by certain drug-drug interactions. Polymorphisms of metabolizing pathways, including CYP, and efflux transporters, such as MDR1 and SLCO1B1, may cause intersubject variability in plasma statin levels and therefore may be responsible for susceptibility to myopathy. The aim of this review is to summarize selected genetic polymorphisms that predispose to statin-related myopathy (including combined studies of myopathy and myalgia). Genome-wide studies suggest that there is a strong candidate variant within the SLCO1B1 gene (rs4149056) for statin-associated myopathy in a UK (European) population. An enhanced understanding of statin-related myopathy may lead to safer drug development and use.

[35] *Wilke RA*. **Translational pharmacogenetics and risk management in the cardiovascular arena: CYP3A5*3 model for gene-based drug selection**. Personalized medicine 2006; 3:385-390.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29788593
ABSTRACT
The clinical community is moving rapidly toward the prospective application of gene-based drug dosing. Specifically within the cardiovascular arena, the cytochrome P450 (CYP)3A5*3 allele may represent an optimal starting point. All CYP3A5*3 alleles contain an A6986G transition in intron 3, which reduces enzyme expression through the introduction of a premature stop codon. The current review explores four potential reasons why the clinical and scientific communities should consider including CYP3A5*3 in any panel of gene polymorphisms developed for the purpose of guiding cardiovascular pharmacotherapy: the CYP3A enzyme family metabolizes nearly half of all prescription drugs; the CYP3A enzyme family metabolizes several drugs utilized for primary and secondary risk reduction in the context of coronary artery disease; the CYP3A5*3 allele has been associated with differential outcomes related to lipid lowering therapy; and the CYP3A5*3 allele is highly prevalent in all populations studied to date.

Literature update week 21 (2018)

[36] *Maillart E*. **Treatment of progressive multiple sclerosis: Challenges and promising perspectives**. Revue neurologique 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29779852
ABSTRACT
Management of progressive multiple sclerosis (MS) is one of the main challenges of the new century. Based on our knowledge of pathophysiology, three therapeutic strategies are proposed: anti-inflammatory (ocrelizumab, siponimod...); remyelinating (opicinumab); and neuroprotective (high-dose biotin, ibudilast, simvastatin...). Nevertheless, despite recent promising positive clinical trials, new methodological approaches for therapeutic protocols with adaptable outcomes to assess progression are still needed.

[37] *Auer J, Berent R*. **Alirocumab as add-on therapy to statins: current evidence and clinical potential**. Therapeutic advances in cardiovascular disease 2018:1753944718775352.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29792380
ABSTRACT
Atherosclerotic cardiovascular diseases (ASCVDs) are associated with a substantial mortality, physical morbidity, and mental disability. Elevated plasma low-density lipoprotein cholesterol (LDL-C) levels play a major role in the pathophysiology of ASCVDs. Statins have been shown to reduce ASCVD risk and associated events and are recommended as first-line therapy for treatment of hypercholesterolemia by current international guidelines. The key issue is to attain guideline-recommended LDL-C levels (below 70 mg/dl) for patients at very high cardiovascular risk. However, many high-risk and very-high-risk patients on statin therapy remain beyond treatment goals despite lifestyle modification and statins, and are exposed to a high risk of future cardiovascular events including myocardial infarction (MI), stroke, revascularization procedures, and death. This clearly emphasizes the urgent need for additional LDL-C reduction with new therapeutic strategies to target these highly atherogenic particles and to further reduce the burden of ASCVDs. Proprotein convertase subtilisin/kexin type 9 (PCSK9) plays a major role as a key regulator of the hepatic LDL receptor recycling process. Developments over the past 15 years have demonstrated PCSK9 inhibition to be a novel therapeutic strategy to manage increased LDL-C levels. A number of clinical studies using humanized monoclonal antibody technology against PCSK9 have shown profound reductions of LDL-C levels when used either alone or in combination with statin therapy. Recently, the first cardiovascular outcome study demonstrated a significant reduction of ASCV events when evolocumab was added to a statin therapy. This review will discuss current knowledge about antibody-mediated PCSK9 inhibition as add-on therapy to statin and the clinical potential that may be expected.

[38] *Maksymets T, Karpyshyn N, Gutor T et al.* **Influence of risk factors on insulin resistance in patients with overweight and obesity**. Wiadomosci lekarskie (Warsaw, Poland : 1960) 2018; 71:558-560.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29783224
ABSTRACT
OBJECTIVE: Introduction: Obesity is a multifactorial, heterogenic disease, associated with an increased risk of morbidity and mortality due to cardiovascular diseases, diabetes, cancer,

chronic liver and kidney diseases. Excessive body weight and obesity are serious medical and social problems, since their incidence is constantly increasing and has reached global epidemic proportions. The aim: Determining the influence of risk factors on insulin resistance level in patients with overweight and obesity. PATIENTS AND METHODS: Materials and methods: The study included 127 patients with overweight and obesity. Anthropometric measurement was performed for determination of the degree and type of obesity by WHO and IDF (2015) criteria. The levels of ALT, AST, uric acid, lipids, glucose, insulin, glycated hemoglobin in the blood were measured. HOMA-IR index was calculated and multiple regression method with inclusion of reliable signs was applied. RESULTS: Results: By multiple regression method, we identified four signs which, in combined action, affect HOMA-IR index: AST, triglycerides, insulin level and atorvastatin dose. Value of determination coefficient indicates that the level of insulin resistance in overweight and obese patients is by 37% explained by the factors included in regressive model. However, we did not investigate the influence of behavioral risk factors and burdened family history of type 2 diabetes mellitus, which significantly affect insulin resistance level. CONCLUSION: Conclusions: We assume that modification of lifestyle and individual approach to pharmacologic correction of dyslipidemia in overweight and obese patients help to avoid the development of insulin resistance, which is a predictor of type 2 diabetes mellitus.

[39] *Zhang K, Liu G, Tian F, Zhang L*. **[REGUL ATORY EFFECT OF SIMVASTATIN ON MIDDLE/L ATE STAGES OSTEOGENIC DIFFERENTIATION OF BONE MARROW MESENCHYMAL STEM CELLS VIA p38MAPK PATHWAY]**. Zhongguo xiu fu chong jian wai ke za zhi = Zhongguo xiufu chongjian waike zazhi = Chinese journal of reparative and reconstructive surgery 2016; 30:1038-1043.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29786238

ABSTRACT

OBJECTIVE: To investigate the regulatory effect of simvastatin on osteogenic differentiation of bone marrow mesenchymal stem cells (BMSCs) at middle/late stages by p38MAPK pathway under condition of osteoinductive environment. METHODS: The bone marrow of bilateral femur and tibia were harvested from 20 4-week-old female Sprague Dawley rats. BMSCs were isolated and cultured with whole bone marrow culture method; the second generation of cells were randomly divided into 5 groups: control group (complete medium, CM), simvastatin group (simvastatin medium, SIM), osteogenic induction group (osteogenic induction medium, OM), simvastatin and osteogenic induction group (simvastatin+osteogenic induction medium, OM+SIM), and blocker group (SB203580+simvastatin+osteogenic induction medium, OM+SIM+SB). MTT assay was used to detect the cell activity in CM group and SIM group at 2, 3, 4, 5, and 6 days, ELISA method to measure the content of alkaline phosphatase (ALP) in OM group and OM+SIM group at 7 and 14 days. The mRNA and protein expressions of osteocalcin (OCN) were detected by real-time quatitative PCR and Western blot after 1, 12, and 24 hours of osteogenic induction at 21 and 28 days. The protein expressions of phospho-p38 (p-p38) and p38 in OM group, OM+SIM group, and OM+SIM+SB group were detected by Western blot at the best induction time of simvastatin. RESULTS: MTT assay showed that no significant difference was found in absorbance (A) value between CM group and SIM group at each time point (P>0.05), indicating no effect of 1x10(-7) mol/L simvastatin on cell viability. ELISA results showed that ALP content significantly increased in OM+SIM group when compared with OM group at 7 and 14 days; the ALP content was significantly higher at 7 days than 14 days in OM

group and OM+SIM group (P<0.05). OCN mRNA and protein expressions at 12 hours were significantly higher than those at other time points in each group (P<0.05), and the expressions of OM+SIM group was significantly higher than those of OM group (P<0.05). The best induction time of simvastatin was 12 hours. At 12 hours after blocking intervention, the p-p38/p38 in OM+SIM+SB group was significantly lower than that in OM group and OM+SIM group (P<0.05), and the p-p38/p38 in OM+SIM group was significantly higher than that in OM group (P<0.05). CONCLUSIONS: Simvastatin can increase the mRNA and protein expression levels of OCN and the protein of p-p38 in osteogenic differentiation of BMSCs at middle/ late stages, and its best induction time is 12 hours.