Literature update week 40 (2018)

[1] *Li YH, Chao TH, Liu PY et al.* **Lipid Lowering Therapy for Acute Coronary Syndrome and Coronary Artery Disease: Highlights of the 2017 Taiwan Lipid Guidelines for High Risk Patients**. Acta Cardiologica Sinica 2018; 34:371-378.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30271086
ABSTRACT
Intensive lipid lowering therapy is important in patients with acute coronary syndrome (ACS) and stable coronary artery disease (CAD). The 2017 Taiwan Lipid Guidelines for High Risk Patients was recently published. The guideline suggests that low-density lipoprotein cholesterol (LDL-C) should be the primary target, and that the treatment goal of LDL-C is < 70 mg/dL for patients with ACS or stable CAD. A lower target of < 55 mg/dL is appropriate for patients with ACS and diabetes mellitus. Non-high-density lipoprotein cholesterol (non-HDL-C) < 100 mg/dL can be considered as the secondary target after achieving the LDL-C goal for patients with a triglyceride level > 200 mg/dL. Statins are usually the first-line therapy. Moderate or high intensity statins are preferred, and up-titration to the highest recommended and tolerable dose to reach the target is necessary. Combination therapy with statins and other lipid-lowering drugs can also be considered. We hope the clinical outcomes of patients with ACS or CAD can be improved in Taiwan through the implementation of the guideline recommendations.

[2] *Kawada-Watanabe E, Yamaguchi J, Kanbayashi K et al.* **Predictive Value of Baseline High-Sensitivity C-Reactive Protein Level and Renal Function for Patients With Acute Coronary Syndrome Undergoing Aggressive Lipid-Lowering Therapy: A Subanalysis of HIJ-PROPER**. The American journal of cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30270178
ABSTRACT
The systematic inflammatory response might confound renal impairment, and both have been reported to affect clinical outcomes after acute coronary syndrome. We examined the impacts of the high-sensitivity C-reactive protein (hsCRP) level and estimated glomerular filtration rate level on the prognosis for acute coronary syndrome patients who underwent aggressive lipid-lowering therapy in contemporary practice. This was a subanalysis of the HIJ-PROPER study, and 1,734 patients were enrolled. Patients were divided into 4 groups using an hsCRP value of 10mg/L and an estimated glomerular filtration rate value of 60 ml/min/1.73 m(2) as the cut-off points. Groups were defined as follows: group A, low hsCRP and normal or mild renal impairment; group B, low hsCRP and renal impairment; group C, high hsCRP and normal or mild renal impairment; and group D, high hsCRP and renal impairment. The primary end point was defined as the composite of all-cause death, nonfatal myocardial infarction, nonfatal stroke, and unstable angina or coronary revascularizations. The median follow-up period was 3.9years, and the follow-up rate was 99%. Compared with group A, the 2 higher hsCRP groups (groups C and D) showed a significantly higher incidence of primary end points (hazard ratio 1.36, 95% confidence interval 1.12 to 1.65, p=0.002; and hazard ratio 1.40, 95% CI 1.10 to 1.80, p=0.008). Such a difference was not found compared with group B. In conclusion, patients with higher hsCRP levels had worse prognoses regardless of renal impairment and aggressive lipid-lowering therapy.

[3] *Wang HY, Jiao QP, Chen SY et al.* **Efficacy and Safety of Policosanol Plus Fenofibrate Combination Therapy in Elderly Patients with Mixed Dyslipidemia: A Randomized, Controlled Clinical Study**. The American journal of the medical sciences 2018; 356:254-261.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30286820
ABSTRACT
BACKGROUND: Policosanol is a mixture of long-chain alcohols isolated from sugar cane. This controlled, randomized clinical trial was designed to compare the efficacy and safety of fenofibrate, policosanol and a combination of these 2 in lowering low-density-lipoprotein cholesterol (LDL-C) in elderly patients with mixed dyslipidemia. METHODS: A total of 102 patients aged >/=60years were randomly assigned into 3 groups: patients receiving a 24-week therapy of fenofibrate (200 mg/day), policosanol (20 mg/day) or fenofibrate+policosanol combination. Lipids were evaluated at baseline, after 16 and after 24 weeks of therapy. Brachial-ankle pulse wave velocity (ba-PWV) was performed, and SF-36 questionnaires were used to evaluate the patients' quality of life. The primary endpoint was the percentage reduction in LDL-C. The secondary end points included percentage change in nonhigh density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC), triglyceride, high-density-lipoprotein cholesterol (HDL-C), ba-PWV and SF-36 scores. Safety was assessed by adverse events and laboratory parameters. RESULTS: LDL-C, non-HDL-C and TC were decreased, respectively after treatment with policosanol for 24 weeks ($P < 0.01$). Treatment with policosanol+fenofibrate resulted in significantly greater reductions in TC, non-HDL-C and LDL-C compared to fenofibrate alone ($P < 0.01$, respectively). There were significant increases in SF-36 scores in the policosanol and policosanol+fenofibrate groups ($P < 0.05$), and significant improvements of ba-PWV in the 2 groups ($P < 0.01$). There were no serious adverse events or significant changes in laboratory variables after any of the treatment regimens. CONCLUSIONS: Policosanol+fenofibrate combination therapy significantly improved lipid parameters, arterial stiffness, and quality of life, with good tolerability.

[4] *Rosas Saldarriaga D, Berrouet Mejia MC*. **Atorvastatin-Associated DRESS Syndrome**. American journal of therapeutics 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30272596
ABSTRACT

[5] *Chemaly P, Nallet O, Delarche N et al.* **[Screening for familial hypercholesterolemia from low-density lipoprotein cholesterol levels at admission in the coronary care unit]**. Annales de cardiologie et d'angeiologie 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30290906
ABSTRACT
BACKGROUND: Familial hypercholesterolemia (FH) is a frequent genetic disorder that leads to premature atherosclerosis and coronary artery disease. However, knowledge of FH by cardiologists is weak, and FH remains underdiagnosed in France. FH should be suspected when low-density lipoprotein cholesterol (LDLc) levels exceed 1.9g/L (4.9mmol/L) without lipid lowering therapy. PURPOSE: This multicenter retro- and prospective observational study aimed at estimating the prevalence of high LDLc levels in patients admitted in coronary care units, and the impact for the personal and familial follow-up for lipid status. METHODS: Retrospective

analysis of all plasma lipid measurements performed at admission in coronary care unit of 4 hospitals in 2017. Retrospective analyses of demographic, clinical, and coronary data of consecutive patients with LDLc levels>/=1.9g/L. Prospective 1 year follow-up focused on lipid levels, treatments, and personal and familial screening for FH. RESULTS: Lipid measurement has been performed in 2172 consecutive patients, and 108 (5%) had LDLc level>/=1.9g/L (mean age 64+/-14 years, men 51%). The primary cause of the hospitalisation was acute coronary syndrome (78%), and 22% of patients were free off coronary artery disease. Lipid lowering therapy was present in 9% of patients at admission, and 84% at discharge, with high statins regimen. At 1-year follow-up, control of LDLc level was not performed in 20% of patients, and statin dose was decreased (36%) or withdrawn (7%) in 43%. Lipid measurement has been performed in at least one first degree relative in 37% of patients, and genetic exploration has been done for 3 patients. CONCLUSIONS: Screening of FH in CCU should be routinely performed using the Dutch Score when LDLc is above 1.9g/L. Individual and familial management of patients at high risk for FH screened in CCU should be optimized, both for diagnosis and therapeutic purposes.

[6] *Kuhlman AB, Morville T, Dohlmann TL et al.* **Coenzyme Q10 does not improve peripheral insulin sensitivity in statin-treated men and women; the LIFESTAT study**. Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30273493

ABSTRACT

Simvastatin is a cholesterol-lowering drug that is prescribed to lower the risk of cardiovascular disease following high levels of blood cholesterol. There is a possible risk of new onset diabetes mellitus with statin treatment but the mechanisms behind are unknown. Coenzyme Q10 (CoQ10) supplementation has been found to improve glucose homeostasis in various patient populations and may increase muscle GLUT4 content. Our aim was to investigate whether eight weeks of CoQ10 supplementation can improve glucose homeostasis in simvastatin treated subjects. Thirty-five men and women in treatment with minimum 40 mg of simvastatin daily were randomized to receive either 2 x 200 mg/d of CoQ10 supplementation or placebo for eight weeks. Glucose homeostasis was investigated with fasting blood samples, OGTT and IVGTT. Insulin sensitivity was assessed with the hyperinsulinemic, euglycemic clamp. Different indices were calculated from fasting samples and OGTT as secondary measures of insulin sensitivity. A muscle biopsy was obtained from the vastus lateralis muscle for muscle protein analyzes. There were no changes in body composition, fasting plasma insulin, fasting plasma glucose or 3hr-glucose with intervention, but HbA1c decreased with time. Glucose homeostasis measured as the AUC for glucose, insulin and C-peptide during OGTT was unchanged after intervention. Insulin secretory capacity was also unaltered after CoQ10 supplementation. Insulin sensitivity was unchanged but hepatic insulin sensitivity (HOMA2-%S) increased. No changes in muscle GLUT4 content was observed after intervention. CoQ10 supplementation does not change muscle GLUT4 content, insulin sensitivity or secretory capacity, but hepatic insulin sensitivity may improve.

[7] *Yang N, Dong B, Yang J et al.* **Effects of Rosuvastatin on Apolipoprotein J in Balloon-Injured Carotid Artery in Rats**. Arquivos brasileiros de cardiologia 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30281685

ABSTRACT

BACKGROUND: Restenosis after percutaneous coronary intervention in coronary heart disease remains an unsolved problem. Clusterin (CLU) (or Apolipoprotein [Apo] J) levels have been reported to be elevated during the progression of postangioplasty restenosis and atherosclerosis. However, its role in neointimal hyperplasia is still controversial. OBJECTIVE: To elucidate the role Apo J in neointimal hyperplasia in a rat carotid artery model in vivo with or without rosuvastatin administration. METHODS: Male Wistar rats were randomly divided into three groups: the control group (n = 20), the model group (n = 20) and the statin intervention group (n = 32). The rats in the intervention group were given 10mg /kg dose of rosuvastatin. A 2F Fogarty catheter was introduced to induce vascular injury. Neointima formation was analyzed 1, 2, 3 and 4 weeks after balloon injury. The level of Apo J was measured by real-time PCR, immunohistochemistry and western blotting. RESULTS: Intimal/medial area ratio (intimal/medial, I/M) was increased after balloon-injury and reached the maximum value at 4weeks in the model group; I/M was slightly increased at 2 weeks and stopped increasing after rosuvastatin administration. The mRNA and protein levels of Apo J in carotid arteries were significantly upregulated after rosuvastatin administration as compared with the model group, and reached maximum values at 2 weeks, which was earlier than in the model group (3 weeks). CONCLUSION: Apo J served as an acute phase reactant after balloon injury in rat carotid arteries. Rosuvastatin may reduce the neointima formation through up-regulation of Apo J. Our results suggest that Apo J exerts a protective role in the restenosis after balloon-injury in rats.

[8] *Barter PJ, Cochran BJ, Rye KA*. **CETP inhibition, statins and diabetes**. Atherosclerosis 2018; 278:143-146.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30278356

ABSTRACT

Type 2 diabetes is a causal risk factor for the development of atherosclerotic cardiovascular disease (ASCVD). While treatment with a statin reduces the risk of having an ASCVD event in all people, including those with type-2 diabetes, statin treatment also increases the likelihood of new onset diabetes when given to those with risk factors for developing diabetes. Treatment with the cholesteryl ester transfer protein (CETP) inhibitor, anacetrapib, reduces the risk of having a coronary event over and above that achieved with a statin. However, unlike statins, anacetrapib decreases the risk of developing diabetes. If the reduced risk of new-onset diabetes is confirmed in another CETP inhibitor outcome trial, there will be a case for considering the use of the combination of a statin plus a CETP inhibitor in high ASCVD-risk people who are also at increased risk of developing diabetes.

[9] *Beliard S, Boccara F, Cariou B et al.* **High burden of recurrent cardiovascular events in heterozygous familial hypercholesterolemia: The French Familial Hypercholesterolemia Registry**. Atherosclerosis 2018; 277:334-340.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30270068

ABSTRACT

BACKGROUND AND AIMS: Cardiovascular risk is high in heterozygous familial hypercholesterolemia (HeFH). The objective of this study was to describe recurrent

cardiovascular events in selected patients with HeFH attending lipid clinics in France. METHODS: We included 781 patients with a clinical (Dutch Lipid Clinic Network score>/=6) or genetic diagnosis of HeFH who had experienced a first cardiovascular event (myocardial infarction, percutaneous coronary intervention or coronary bypass, unstable angina, stroke, peripheral arterial revascularization or cardiovascular death) and were enrolled in the French Familial Hypercholesterolemia Registry (November 2015 to March 2018). RESULTS: The first cardiovascular event occurred at the mean age of 47 years (interquartile range 39-55) in a predominantly male population (72%); 48% of patients were on statin therapy. Overall, 37% of patients had at least one recurrent cardiovascular event (mean of 1.8 events per patient), of which 32% occurred in the 12 months after the index event; 55% of events occurred >3 years after the first event. Mean LDL-C at the last clinic visit was 144+/-75mg/dL (132+/-69mg/dL for patients on high-potency statin therapy and 223+/-85mg/dL for untreated patients). CONCLUSIONS: The rate of recurrent cardiovascular events was high in French patients with HeFH in secondary prevention. The detection of FH during childhood is crucial to prevent CV events at a young age by early initiating statin therapy. There is a clear urgent need to expand the actual very small target population which can be treated with the PCSK9 inhibitor in France.

[10] *Botha TC, Pilcher GJ, Wolmarans K et al.* **Statins and other lipid-lowering therapy and pregnancy outcomes in homozygous familial hypercholesterolaemia: A retrospective review of 39 pregnancies**. Atherosclerosis 2018; 277:502-507.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30270091
ABSTRACT
BACKGROUND AND AIMS: Pregnancy in HoFH females is associated with further elevation of already markedly elevated low density lipoprotein cholesterol (LDL-C) levels, particularly if lipid-lowering therapy is discontinued, placing the mother and fetus at increased cardiovascular risk. Lipoprotein apheresis is the current recommended treatment for pregnant HoFH patients. However, this is costly, time consuming, and is not available in many countries. Alternative treatment strategies to control hypercholesterolaemia during pregnancy in HoFH patients are necessary. METHODS: This study was a retrospective review of 39 pregnancies from a cohort of 20 genotypically confirmed female HoFH patients. RESULTS: No maternal cardiac complications or deaths occurred during the pregnancies or during the first year postpartum. Twenty five pregnancies were exposed to lipid-lowering therapy, of which 18 were exposed to statin therapy, just prior to or during the pregnancy. Thirty three (84%) pregnancies carried to term, 3 (8%) premature deliveries and 3 (8%) miscarriages were observed. Complications associated with pregnancy in these HoFH patients, did not differ from those reported during pregnancies of otherwise healthy woman. CONCLUSIONS: HoFH is a severe disease impacting significantly on life expectancy. However, for many females with HoFH, despite the high cardiovascular risk, pregnancy is not uncommon. In resource poor settings and when LA is not available, lipid lowering therapy, particularly statin therapy during pregnancy, appears to be safe for both mother and fetus and is an acceptable alternative for LDL-C reduction in these high risk patients.

[11] *Brunham LR, Ruel I, Khoury E et al.* **Familial hypercholesterolemia in Canada: Initial results from the FH Canada national registry**. Atherosclerosis 2018; 277:419-424.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30270080

ABSTRACT

BACKGROUND AND AIMS: Familial hypercholesterolemia (FH) is under-diagnosed and under-treated in most of the world, including Canada. National registries play a key role in identifying patients with FH, understanding gaps in care, and advancing the science of FH to better treat these patients. METHODS: FH Canada has established a national registry across 19 academic sites acting as "hubs" in Canada to increase awareness and access to standard-of-care therapies. RESULTS: To-date, more than 3000 patients with FH have been entered into a secure, web-based database. Early outcomes of this initiative include a greater understanding of treatment gaps for patients with FH in Canada, the development of a new, simplified Canadian definition of FH, and tools to aid in the diagnosis of FH, including imputation of baseline levels of LDL cholesterol. CONCLUSIONS: As the national registry expands in size and scope, further learning will emerge with ultimate benefit for the diagnosis and treatment of FH in Canada.

[12] *Corral P, Geller AS, Polisecki EY et al.* **Unusual genetic variants associated with hypercholesterolemia in Argentina**. Atherosclerosis 2018; 277:256-261.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30270055

ABSTRACT

BACKGROUND AND AIMS: Marked hypercholesterolemia, defined as low density lipoprotein cholesterol (LDL-C) levels>/=190mg/dL, may be due to LDLR, APOB, and PCSK9 variants. In a recent analysis, only 1.7% of cases had such variants. Our goal was to identify other potential genetic causes of hypercholesterolemia. METHODS: In a total of 51,253 subjects with lipid testing, 3.8% had elevated total cholesterol >300mg/dL and/or LDL-C>/=190mg/dL. Of these, 246 were further studied, and 69 without kidney, liver, or thyroid disease and who met Dutch Lipid Clinic Network criteria of >/=6 points had DNA sequencing done at the LDLR, APOB, PCSK9, APOE, LDLRAP1, STAP1, ABCG5, ABCG8, CYP27A1, LIPA, LIPC, LIPG, LPL, and SCARB1 gene loci and also had 10 SNP analysis for a weighted high LDL-C genetic risk score. RESULTS: In the 69 subjects with genetic analyses, the following variants were observed in 37 subjects (53.6%): LDLR (n=20, 2 novel), ABCG5/8 (n=7, 2 novel), APOB (n=3, 1 novel), CYP27A1 (n=3, 1 novel), LIPA (n=2, 1 novel), APOE (n=2), LIPC (n=1, novel), LIPG (n=1, novel), and SCARB1 (n=1); 14 subjects (20.3%) had a high polygenic score, with 4 (5.8%) having no variants. CONCLUSIONS: Our data indicate that in addition to variants in LDLR, APOB, PCSK9, APOE, LDLRAP1, and STAP1, variants in ABCG5/8, CYP27A1, LIPA, LIPC, and LIPG may be associated with hypercholesterolemia and such information should be used to optimize therapy.

[13] *Futema M, Bourbon M, Williams M, Humphries SE*. **Clinical utility of the polygenic LDL-C SNP score in familial hypercholesterolemia**. Atherosclerosis 2018; 277:457-463.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30270085

ABSTRACT

Mutations in any of three genes (LDLR, APOB and PCSK9) are known to cause autosomal dominant FH, but a mutation can be found in only approximately 40% of patients with a clinical diagnosis of FH. In the remainder, a polygenic aetiology may be the cause of the phenotype, due to the co-inheritance of common LDL-C raising variants. In 2013, we reported the development of a 12-SNP LDL-C "SNP-Score" based on common variants identified as LDL-C

raising from genome wide association consortium studies, and have confirmed the validity of this score in samples of no-mutation FH adults and children from more than six countries with European-Caucasian populations. In more than 80% of those with a clinical diagnosis of FH but with no detectable mutation in LDLR/APOB/PCSK9, the polygenic explanation is the most likely for their hypercholesterolaemia. Those with a low score (in the bottom two deciles) may have a mutation in a novel gene, and further research including whole exome or whole genome sequencing is warranted. Only in families where the index case has a monogenic cause should cascade testing be carried out, using DNA tests for an unambiguous identification of affected relatives. The clinical utility of the polygenic explanation is that it supports a more conservative (less aggressive) treatment care pathway for those with no mutation. The ability to distinguish those with a clinical diagnosis of FH who have a monogenic or a polygenic cause of their hypercholesterolaemia is a paradigm example of the use of genomic information to inform Precision Medicine using lipid lowering agents with different efficacy and costs.

[14] *Groselj U, Kovac J, Sustar U et al.* **Universal screening for familial hypercholesterolemia in children: The Slovenian model and literature review**. Atherosclerosis 2018; 277:383-391.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30270075
ABSTRACT
BACKGROUND AND AIMS: Familial hypercholesterolemia (FH) is arguably the most common monogenic disorder in humans, but severely under-diagnosed. Individuals with untreated FH have an over 10-fold elevated risk of cardiovascular complications as compared to unaffected individuals; early diagnosis and timely management substantially reduce this risk. Slovenia has gradually implemented the program of universal FH screening in pre-school children, consisting of a two step approach: (1) universal hypercholesterolemia screening in pre-school children at the primary care level; (2) genetic FH screening in children referred to the tertiary care level according to clinical guidelines (with additional cascade screening of family members). The program is presented in detail. METHODS: We analyzed retrospective data (2012-2016), to assess the efficiency of the universal FH screening program. In that period, 280 children (59.3% female) were referred to our center through the program for having TC>6mmol/L (231.7mg/dL) or >5mmol/L (193.1mg/dL), with a positive family history of premature cardiovascular complications at the universal hypercholesterolemia screening. RESULTS: 170 (57.1% female) of them were fully genotyped, 44.7% had an FH disease-causing variant (28.8% in LDLR gene, 15.9% in APOB, none in PCSK9), one patient was LIPA positive, and 40.9% of the remaining patients carried an ApoE4 isoform; genetic analysis is still ongoing for one-third of the referred patients. For almost every child with confirmed FH, one parent had highly probable FH. CONCLUSIONS: FH was confirmed in almost half of the referred children, detected through the universal screening for hypercholesterolemia.

[15] *Hagger MS, Hardcastle SJ, Hu M et al.* **Effects of medication, treatment, and behavioral beliefs on intentions to take medication in patients with familial hypercholesterolemia**. Atherosclerosis 2018; 277:493-501.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30270090
ABSTRACT

BACKGROUND AND AIMS: Although familial hypercholesterolemia (FH) can be effectively managed using cholesterol-lowering medication, patients often fall short of complete treatment adherence. Identifying the psychological factors associated with self-regulation of FH medication is important to inform interventions to maximize adherence. The aim of the present study was to test an integrated psychological model in predicting FH patients' intentions to take medication. METHODS: FH patients attending clinics in seven countries were invited to participate in a cross-sectional survey study. Consenting patients (N=551) completed self-report measures of generalized beliefs about medication overuse and harms, beliefs in treatment effectiveness, specific beliefs about taking medication (attitudes, subjective norms, perceived behavioral control), and intentions to take medication. Participants also completed measures of demographic variables (age, gender, education level, income, cardiovascular disease status). Data were analysed using path analysis controlling for country and demographic variables. RESULTS: Attitudes (beta=.331, p<0.001), subjective norms (beta=.121, p=0.009), and beliefs about medication overuse (beta=-.160, p<0.001) were significant predictors of intentions to take medication. Treatment beliefs predicted intentions indirectly (beta=.088, p<0.001) through attitudes and subjective norms. There was also an indirect effect of beliefs about medication overuse on intentions (beta=-.045, p=0.056), but the effect was small compared with the direct effect. CONCLUSIONS: The findings indicate the importance among FH patients of specific beliefs about taking medication and generalized beliefs about medication overuse and treatment in predicting medication intentions. When managing patients, clinicians should emphasize the efficacy of taking cholesterol-lowering drugs and the importance of treatment outcomes, and allay concerns about medication overuse.

[16] *Hsiung YC, Lin PC, Chen CS et al.* **Identification of a novel LDLR disease-causing variant using capture-based next-generation sequencing screening of familial hypercholesterolemia patients in Taiwan**. Atherosclerosis 2018; 277:440-447.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30270083
ABSTRACT
BACKGROUND AND AIMS: Familial hypercholesterolemia (FH) is an autosomal dominant disorder with paramount health impacts. However, less than 1% FH patients in Taiwan were formally diagnosed, partly due to the lack of reliable cost-effective genetic testing. We aimed at using a next-generation sequencing (NGS) platform as the clinical genetic testing method for FH. METHODS: We designed probes to capture the whole LDLR gene and all coding sequences of APOB and PCSK9, and then sequenced with Illumina MiSeq platform (2x300 bps). The entire pipeline was tested on 13 DNA samples with known causative variants (including 3 large duplications and 2 large deletions). Then we enrolled a new cohort of 28 unrelated FH patients with Dutch Lipid Clinic Network score >/=5. Relatives were included in the cascade screening. RESULTS: From the 13 DNA samples, we correctly identify all the variants, including big duplications and deletions. From the new cohort, we identified the causative variants in 21 of the 28 unrelated probands; five of them carrying a novel splice site variant c.1186+2T>G in LDLR. Among the family members, the concentration of LDL cholesterol was 7.82+/-2.13mmol/l in LDLR c.1186+2T>G carrier group (n = 26), and was significantly higher than 3.18 +/- 1.36 mmol/l in the non-carrier group (n = 25). CONCLUSIONS: This is the first capture-based NGS testing for FH to cover the whole LDLR genomic region, and therefore making reliable structural

variation detection. This panel can comprehensively detect disease-causing variants in LDLR, APOB, and PCSK9 for FH patients.

[17] *Latkovskis G, Saripo V, Gilis D et al.* **Latvian registry of familial hypercholesterolemia: The first report of three-year results**. Atherosclerosis 2018; 277:347-354.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30270070
ABSTRACT
BACKGROUND AND AIMS: Familial hypercholesterolemia (FH) was rarely diagnosed in Latvia before 2015, when the Latvian Registry of FH (LRFH) was established. Here, we report the first experience of the LRFH over three years (2015-2017). METHODS: The LRFH is an ongoing nationwide, dynamic, long-term prospective cohort. The diagnosis of FH was assessed using the Dutch Lipid Clinic Network (DLCN) criteria. Cascade screening of first-degree relatives using age- and sex-specific percentiles of low-density lipoprotein cholesterol (LDL-C) was performed in relatives of patients with definite and probable FH. RESULTS: Among the 416 individuals included in the LRFH, 181 patients were diagnosed with FH (140 index cases and 41 relatives) and 151 with possible FH (not analysed in this report). The mean age was 51.3+/-14.1 years, 38.1% (n=69) were men and 35.4% (n=64) had a history of premature coronary heart disease. Only 54.1% (n=98) of patients were on any lipid-lowering therapy before inclusion in the LRFH. The maximal statin dose was used by 23.2% (n=42), and only 4.4% (n=8) had their LDL-C levels below the goal. The initial mean total and LDL-C levels were 7.7+/-2.2 and 5.5+/-2.1mmol/L, respectively. In a subgroup of patients (n=49) with follow-up, LDL-C levels were reduced from 6.1+/-2.1 to 3.6+/-1.7mmol/L ($p < 0.001$). CONCLUSIONS: An estimated 2.3% of FH patients in Latvia were diagnosed within three years. The vast majority of FH patients were under-recognized and poorly treated before their inclusion in the LRFH. Specialized care of FH patients within the frames of the registry substantially improved the management of this high-risk group.

[18] *Pang J, David Marais A, Blom DJ et al.* **Heterozygous familial hypercholesterolaemia in specialist centres in South Africa, Australia and Brazil: Importance of early detection and lifestyle advice**. Atherosclerosis 2018; 277:470-476.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30270087
ABSTRACT
BACKGROUND AND AIMS: Familial hypercholesterolaemia (FH) is the commonest monogenic disorder that accelerates atherosclerotic cardiovascular disease. We compared and contrasted the characteristics of patients from three specialist centres in the southern hemisphere. METHODS: Adult index-cases with molecularly diagnosed heterozygous FH attending specialist lipid centres in Cape Town, Perth and Sao Paulo were studied. Myocardial infarction, revascularisation, hypertension, diabetes, smoking and lipid-lowering treatment were recorded at the time of diagnosis and compared across the three centres. RESULTS: The spectrum of genetic variants causative of FH was significantly different in patients attending the centres in South Africa compared with Australia and Brazil. Hypertension and diabetes were more prevalent in Brazilian and Australian patients, than in South African patients, but the frequency of smoking was significantly greater in South Africa than the other two centres ($p<0.01$). Age, male sex and smoking were significant independent predictors of coronary artery disease (CAD)

in all three countries (p<0.05). CONCLUSIONS: Patients with FH in three specialist centres in the southern hemisphere exhibit a high prevalence of non-cholesterol cardiovascular disease risk factors. Older age, male sex and smoking were more common among subjects with CAD. In all three countries, there should be vigorous programmes for the control of risk factors beyond good control of hypercholesterolaemia among patients with FH. Promotion of a healthy lifestyle, especially anti-smoking advice, is of paramount importance.

[19] *Raal FJ, Hovingh GK, Catapano AL*. **Familial hypercholesterolemia treatments: Guidelines and new therapies**. Atherosclerosis 2018; 277:483-492.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30270089
ABSTRACT
Familial hypercholesterolemia (FH) is a genetic disorder resulting from mutations in genes encoding proteins involved in the metabolism of low density lipoproteins (LDL) and characterized by premature cardiovascular disease due to the exposure to high levels of LDL-cholesterol (LDL-C) from birth. Thus, the early identification of FH subjects, followed by appropriate treatment is essential to prevent or at least delay the onset of cardiovascular events. However, FH is largely underdiagnosed; in addition, FH patients are frequently not adequately treated, despite the availability of several pharmacological therapies to significantly reduce LDL-C levels. Current guidelines recommend LDL-C targets for FH (either heterozygotes [HeFH] or homozygotes [HoFH]) <100mg/dL (<2.6mmol/L) for adults or <70mg/dL (<1.8mmol/L) for adults with CHD or diabetes, and <135mg/dL (<3.5mmol/L) for children. With the pharmacological options now available, which include statins as a first approach, ezetimibe, and the recently approved monoclonal antibodies targeting PCSK9, the guideline recommended LDL-C target levels can be achieved in the majority of heterozygous FH subjects, while for the most severe forms of homozygous FH, the addition of therapies such as lomitapide either with or without apheresis may be required.

[20] *Schmidt N, Dressel A, Grammer TB et al.* **Lipid-modifying therapy and low-density lipoprotein cholesterol goal attainment in patients with familial hypercholesterolemia in Germany: The CaReHigh Registry**. Atherosclerosis 2018; 277:314-322.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30270065
ABSTRACT
BACKGROUND AND AIMS: Familial hypercholesterolemia (FH) is amongst the most common genetic disorders encountered in primary care. Yet, only a minority of affected patients is diagnosed and treated. This interim analysis of the CaRe High Registry aims at examining the state of treatment and attainment of lipid goals in German FH patients. METHODS: The CaRe High registry includes FH patients from lipid clinics and private practices. Data have been collected using questionnaires filled in by the recruiting physicians and by interviewing the participating patients. RESULTS: We examined 512FH patients diagnosed according to clinical criteria. Median age at the time of the first FH diagnosis was 39 (25th and 75th percentile: 27-50) years, median treatment naive LDL cholesterol (LDL-C) was 239.4mg/dl (6.19mmol/l), 25th to 75th percentile 191.8-342.5mg/dl (4.96-8.86mmol/l). 27% of the participants did not receive lipid-lowering drugs. Among the patients treated with lipid-lowering drugs, 19% received a PCSK9 inhibitor (PCSK9i) in combination with a statin, 9% were treated with a PCSK9i alone and

3% were treated with a combination of PCSK9i and a non-statin drug. Patients with pre-existing CVD were more likely to be treated with lipid-lowering drugs and more likely to receive a PCSK9i, but LDL-C targets were only achieved by a minority of patients (<20%). Gap to target LDL-C was lowest and the median achieved LDL-C reduction was 1.4 times higher with PCSK9i treatment than with (oral) lipid-lowering therapy without PCSK9i. CONCLUSIONS: The Care High registry has included patients with the typical clinical features of familial hypercholesterolemia. PCSK9i treatment in addition to standard therapy allows attainment of target values in many patients with initially very high LDL-C.

[21] *Shek A, Alieva R, Kurbanov R et al.* **Burden of familial heterozygous hypercholesterolemia in Uzbekistan: Time is muscle**. Atherosclerosis 2018; 277:524-529.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30270094
ABSTRACT
BACKGROUND AND AIMS: We aimed to assess the disease burden and to study the molecular genetic characteristics of heterozygous familial hypercholesterolemia (HeFH) patients within the Uzbek population to develop a program of early disease detection and effective treatment measures. METHODS: 201 patients were included in the study, of whom 57 with chronic stable coronary artery disease (SCAD) and HeFH, and 144 with SCAD without HeFH belonging to the control group, and divided into two subgroups: A, statin free before the study (n=63) and B (n=81), who took statin outpatiently. We applied the Dutch Lipid Clinic Network Criteria (DLCN) to diagnose HeFH. Serum level of PCSK-9 was measured with the ELISA Kit. The genetic typing at PCSK9 E670G (rs505151) polymorphism was performed with the PCR-RFLP method. RESULTS: Underestimation of early lipid studies and inadequate treatment in HeHF patients within the Uzbek population are accompanied by a 1.8-time increase of more frequent history of myocardial infarction (p<0.05), a 3-time stroke (p<0.05) and 2-time percutaneous coronary intervention (p<0.05). The study of genotypes and alleles of PCSK9 E670G (rs505151) polymorphism allowed to state that small es, Cyrillicarriage of the <<damaging>>allele G in SCAD and HeHF patients was 2 times higher (11.4%), than in non HeHF (6.0%) and 3 times (3.0%) than in healthy ones, but the differences were not significant. Herewith, G-carriership is accompanied by a higher incidence of myocardial infarction (p<0.05) and stroke (p<0.05), coronary artery bypass grafting in anamnesis (p<0.001), and number of plaques in carotids (p<0.05). In group I of SCAD patients with HeFH, 18 (31.6%) cases of diabetes mellitus were observed, which did not exceed their number in group II (48, 33.3%). However, most of them were carriers of the G allele (82.0%, p<0.001). Despite treatment with rosuvastatin 20-40mg/day, in HeHF patients after 3 months, the level of total cholesterol (p<0.001) and LDL-C (p<0.001) was significantly higher than in the control group. CONCLUSIONS: Improvement of early diagnosis of FH, including genetic confirmation, and preventional high-intensity statin therapy or a combination of statins with ezetimibe to achieve the target level of LDL-C, is the closest tactical objective for prevention of MACE within the Uzbek population.

[22] *Soran H, Adam S, Durrington PN*. **Optimising treatment of hyperlipidaemia: Quantitative evaluation of UK, USA and European guidelines taking account of both LDL cholesterol levels and cardiovascular disease risk**. Atherosclerosis 2018; 278:135-142.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30273874

ABSTRACT
BACKGROUND AND AIMS: Guidelines for cholesterol-lowering medication either advocate fixed dose statin treatment without low density lipoprotein (LDL) cholesterol targets or treatment aimed at LDL cholesterol goals. The decrease in LDL cholesterol concentration determines the reduction in atherosclerotic cardiovascular disease (CVD) risk. METHODS: As indices of the effectiveness of reductions in LDL cholesterol concentration achieved by the various guidelines, the number of CVD events prevented in 100 people during 10 years of treatment (N100) and the number of people, who must be treated for 10 years to prevent one CVD event (NNT), were calculated taking into account both CVD risk and pretreatment LDL cholesterol concentration. That our method of calculating NNT and N100, could be extended to statin regimens of different intensity or of statin combined with adjunctive cholesterol-lowering medication was demonstrated by meta-analysis. RESULTS: Reductions in LDL-cholesterol concentration are determined by the choice and dose of medication and by the pre-treatment LDL-cholesterol concentration. At similar CVD risk, whatever cholesterol-lowering strategy is adopted, people with higher pre-treatment LDL cholesterol benefit more than those with lower levels. Fixed dose statin regimens are less effective than target LDL cholesterol levels of 1.8 or 1.4mmol/l when pre-treatment LDL-cholesterol levels exceed 4mmol/l. However, fixed dose statin is more effective in people with lower initial LDL cholesterol. The predicted NNT and N100 were closely related to the observed reduction in CVD risk in our meta-analysis. CONCLUSIONS: In hypercholesterolaemia, aiming for LDL cholesterol targets with statin dose titration (and when necessary adjunctive medication) is essential to optimise benefit.

[23] *Souto AC, Miname MH, Fukushima J et al.* **Health related quality of life in individuals at high risk for familial hypercholesterolemia undergoing genetic cascade screening in Brazil**. Atherosclerosis 2018; 277:464-469.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30270086

ABSTRACT
BACKGROUND AND AIMS: Familial hypercholesterolemia (FH) is a genetic disorder associated with high risk of early major cardiovascular events (MACE) that can impact the health related quality of life (HRQoL), however, this association is unclear. This study evaluated HRQoL in index cases (IC) and first-degree relatives (FDR) of individuals at high risk of FH undergoing genetic cascade screening. METHODS: Data collection was performed before awareness of molecular diagnosis results. Individuals were divided into four groups according to the molecular diagnosis: IC with (IC+) and without (IC-) identified mutations (n = 93 and n = 175, respectively), and affected (FDR+, n = 231) and non-affected (FDR-, n = 159) FDR of IC+. HRQoL measurements, mental (MCS) and physical component (PCS) scores were carried out with SF-12 questionnaire. Associations were tested by generalized linear models. RESULTS: The mean age was 49+/-15 years, 42.2% were men, MACE had occurred in 30.7%. Overall, both PCS and MCS did not differ between FH and non-FH individuals, however, IC trended to have lower PCS independent of FH presence (p=0.003). Lower PCS were associated with female sex (p=0.018), lower education (p<0.001), professional inactivity (p=0.028), previous MACE occurrence (p<0.001), hypertension (p=0.016), depression (p<0.001) and obesity (p<0.001). Lower MCS were associated with female sex (p=0.009), previous MACE occurrence (p=0.034), depression (p<0.001) and smoking (p=0.009). Neither the presence of FH causing mutations nor

pharmacological lipid lowering treatment was associated with HRQoL. CONCLUSIONS: HRQoL is not reduced in both IC and FDR FH individuals in comparison with their non-affected counterparts. Previous MACE and co-morbidities are associated with reduced HRQoL.

[24] *Truong TH, Kim NT, Nguyen MNT et al.* **Homozygous familial hypercholesterolaemia in Vietnam: Case series, genetics and cascade testing of families**. Atherosclerosis 2018; 277:392-398.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30270076
ABSTRACT
BACKGROUND AND AIMS: Familial hypercholesterolaemia has not been previously described in the Vietnamese population. We aimed to describe the features of patients with homozygous familial hypercholesterolaemia (hoFH) in Vietnam and the outcomes of screening family members using genetic and cholesterol testing. METHODS: Mutation testing by massively parallel sequencing for genes causative of FH was undertaken in five index cases presenting to a single cardiac center with a presumptive diagnosis of hoFH. Cascade testing of all available family members was subsequently undertaken. The number of new cases of FH detected and commenced on lipid-lowering treatment was evaluated. RESULTS: All five index cases had true homozygous mutations in the LDL receptor gene (LDLR). Cascade screening was undertaken in four families. 107 relatives were screened and FH was identified in 56 relatives (52%), including 3 new cases of hoFH. Only 5 FH relatives (9%) were subsequently treated owing to the adverse perceptions and comparative high cost of drug treatment, and lack of awareness of FH among patients and local doctors. CONCLUSIONS: HoFH due to LDLR mutations is a severe disorder in Vietnam that needs early detection and treatment with LDL-cholesterol lowering drugs. Cascade testing of families allows effective detection of new cases of FH that may also benefit from early treatment. However, convincing patients to commence statin treatment is a challenge. Extended education and awareness programs and treatment subsidies are imperative to improve the care of patients and families suffering from FH in Vietnam.

[25] *Vallejo-Vaz AJ, De Marco M, Stevens CAT et al.* **Overview of the current status of familial hypercholesterolaemia care in over 60 countries - The EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC)**. Atherosclerosis 2018; 277:234-255.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30270054
ABSTRACT
BACKGROUND AND AIMS: Management of familial hypercholesterolaemia (FH) may vary across different settings due to factors related to population characteristics, practice, resources and/or policies. We conducted a survey among the worldwide network of EAS FHSC Lead Investigators to provide an overview of FH status in different countries. METHODS: Lead Investigators from countries formally involved in the EAS FHSC by mid-May 2018 were invited to provide a brief report on FH status in their countries, including available information, programmes, initiatives, and management. RESULTS: 63 countries provided reports. Data on FH prevalence are lacking in most countries. Where available, data tend to align with recent estimates, suggesting a higher frequency than that traditionally considered. Low rates of FH detection are reported across all regions. National registries and education programmes to improve FH awareness/knowledge are a recognised priority, but funding is often lacking. In

most countries, diagnosis primarily relies on the Dutch Lipid Clinics Network criteria. Although available in many countries, genetic testing is not widely implemented (frequent cost issues). There are only a few national official government programmes for FH. Under-treatment is an issue. FH therapy is not universally reimbursed. PCSK9-inhibitors are available in approximately 2/3 countries. Lipoprotein-apheresis is offered in approximately 60% countries, although access is limited. CONCLUSIONS: FH is a recognised public health concern. Management varies widely across countries, with overall suboptimal identification and under-treatment. Efforts and initiatives to improve FH knowledge and management are underway, including development of national registries, but support, particularly from health authorities, and better funding are greatly needed.

[26] *Vallejo-Vaz AJ, Ray KK*. **Epidemiology of familial hypercholesterolaemia: Community and clinical**. Atherosclerosis 2018; 277:289-297.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30270061
ABSTRACT
Familial hypercholesterolaemia (FH) is a genetic disorder affecting the metabolism of low-density lipoprotein (LDL) particles, leading to high LDL-cholesterol levels maintained over time and higher risk of cardiovascular disease (CVD) early in life. Contemporary studies have challenged prior estimations of FH prevalence and suggest this condition to be more frequent than previously considered, with an overall prevalence rate of 1:200-300 individuals in the general population (1:160,000-300,000 for homozygous FH). However, prevalence of FH varies around the world. In part this is due to an artefact of approaches of detection and methods used to diagnose FH (e.g. lack of gold standard for diagnosis of FH, different criteria applied, availability of genetic testing). But also due to intrinsic characteristic of different populations, e.g. higher presence of founder effects or rates of consanguinity. Additionally, results from many regions are lacking and it is estimated that only a small percentage of subjects with FH would have been diagnosed overall. FH entails a significantly higher risk of CVD, reported to be higher than that estimated by conventional risk assessment tools for the general population. This risk is mainly driven by coronary heart disease. Despite this evidence, low rates of patients meet therapeutic targets for cardiovascular prevention, and implementation of therapy (high intensity statins, combination therapy) is needed. The introduction of novel lipid-lowering therapies may improve this situation. In the present review, we discuss the epidemiology of FH overall, with special attention to different aspects related to prevalence, cardiovascular risk and prognosis, and treatment of FH.

[27] *van Delden XM, Huijgen R, Wolmarans KH et al.* **LDL-cholesterol target achievement in patients with heterozygous familial hypercholesterolemia at Groote Schuur Hospital: Minority at target despite large reductions in LDL-C**. Atherosclerosis 2018; 277:327-333.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30270067
ABSTRACT
BACKGROUND AND AIMS: Familial hypercholesterolemia (FH) is characterized by markedly increased LDL-cholesterol (LDL-C) and premature cardiovascular disease (CVD). LDL-C lowering is the cornerstone of therapy. The aim of our study was to evaluate LDL-C target achievement and explore reasons for not reaching target in FH patients attending a public-sector lipid clinic

at Groote Schuur Hospital in Cape Town, South Africa. METHODS: We reviewed clinical records of patients with genetically confirmed heterozygous FH (heFH) retrospectively. For patients seen after 2013, when new guidelines were published, we determined reasons for use of submaximal therapy. RESULTS: Our study population consisted of 776 adult heFH patients. A substantial proportion (41%) of those younger than 50 years of age had already experienced a cardiovascular event. The mean (+/-SD) untreated and best achieved LDL-C values during follow up were 8.1+/-2.1 and 4.0+/-1.5mmol/l, respectively. Despite a mean LDL-C reduction of 50%, only 140 (25%) achieved an LDL-C</=3.0mmol/l. Of the 164 participants with follow up after 2013, 42 did not reach LDL-C < 3.0mmol/l and did not use maximal therapy (26%). The commonest reasons for not using maximum therapy were statin side-effects (n=15, 36%) and acceptance by the patient (n=9, 22%) or the physician (n=8, 19%) of the control achieved. CONCLUSIONS: The heFH population in Cape Town is characterized by high baseline LDL-C, a high prevalence of CVD at presentation and low rates of achieving an LDL-C target of 3.0mmol/l.

[28] *Vohnout B, Fabryova L, Klabnik A et al.* **Treatment pattern of familial hypercholesterolemia in Slovakia: Targets, treatment and obstacles in common practice**. Atherosclerosis 2018; 277:323-326.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30270066
ABSTRACT
BACKGROUND AND AIMS: Maximal doses of potent statins are the cornerstone of treatment of familial hypercholesterolemia (FH). Despite this, a substantial proportion of FH patients are either under-treated or not treated at all. The aim of this work was to evaluate, in a retrospective study, the treatment of FH patients, the proportion of FH patients reaching low-density lipoprotein cholesterol (LDL-C) goals, and reasons for not reaching LDL-C goals, in 8 lipid clinics in Slovakia dealing with FH patients. METHODS: 201 heterozygous FH patients (50.8+/-14.9 years, 55% females) who attended the lipid clinics at least three times were included in the study. RESULTS: At the first visit, 31.3% of patients were treated with statins and the most common dose was 20mg of atorvastatin, rosuvastatin and simvastatin. At the third visit, 78.1% of patients were treated with statins and 24.4% with ezetimibe. The majority of patients were treated with atorvastatin (75.8%) and rosuvastatin (18.5%) and 31.3% of all patients were treated with atorvastatin 80mg or rosuvastatin 40mg with/without ezetimibe. However, only 11.9% of patients with the LDL-C goal level <2.5mmol/l and 6.9% with the goal <1.8mmol/l reached the level. Reasons for not reaching the goal levels were evaluated by physicians in each patient. Insufficient LDL-C lowering effect of treatment, side-effects of therapy and non-compliance of patients were responsible for 46%, 18% and 30% of cases, respectively. CONCLUSIONS: Referral of FH patients to lipid clinics in Slovakia leads to improvement in the treatment; however, almost 22% of the patients are still without statin treatment and the majority of patients do not reach the LDL-C goal level.

[29] *Vrablik M, Raslova K, Vohnout B et al.* **Real-life LDL-C treatment goals achievement in patients with heterozygous familial hypercholesterolemia in the Czech Republic and Slovakia: Results of the PLANET registry**. Atherosclerosis 2018; 277:355-361.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30270071
ABSTRACT

BACKGROUND AND AIMS: Despite the high prevalence of familial hypercholesterolemia (FH) and available effective lipid-lowering therapy, most of the individuals with this disorder remain undiagnosed and undertreated. The aim of the PLANET registry was to assess the real-life attainment of low-density lipoprotein cholesterol (LDL-C) therapeutic target level in patients with heterozygous FH, to characterize prescribed lipid-lowering therapy with assessment of its efficiency according to the attainment of the target LDL-C level, and to characterize cardiovascular events observed in this patient population again in relation to LDL-C target level attainment. METHODS: PLANET registry was designed as a non-interventional, retrospective, cross-sectional, multicentre disease registry for adult patients with heterozygous FH in the Czech Republic and Slovakia. RESULTS: Overall, 1755 patients were enrolled at 32 sites specialized in FH treatment. 15.4% of patients attained the target LDL-C value. The proportion of patients with LDL-C goal achievement increased to 17.3% in the subgroup of patients receiving high-intensity statin therapy (54.6% of study population). Out of 55 patients receiving inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9), 61.8% reached the LDL-C treatment goal. Of all cardiovascular events reported, 14.0% occurred in patients attaining the LDL-C goal, while it was 86.0% in the not-at-target group. It was documented (p=0.004) that the longer is the patient in care at the specialized FH centre, the higher is the probability that he/she will attain the target LDL-C level. CONCLUSIONS: Although target LDL-C level attainment remains relatively low, the likelihood of LDL-C goal attainment increases with duration of specialized care.

[30] *Yang L, Hernandez RV, Tran TN et al.* **Ordered opening of LDL receptor binding domain of human apolipoprotein E3 revealed by hydrogen/deuterium exchange mass spectrometry and fluorescence spectroscopy**. Biochimica et biophysica acta. Proteins and proteomics 2018; 1866:1165-1173.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30282614
ABSTRACT
Apolipoprotein E3 (apoE3) is an exchangeable apolipoprotein that plays a critical role in cholesterol homeostasis. The N-terminal (NT) domain of apoE3 (residues 1-191) is folded into a helix bundle comprised of 4 amphipathic alpha-helices: H1, H2, H3 and H4, flanked by flexible helices N1 and N2, and Hinge Helix 1 (Hinge H1), at the N-and C-terminal sides of the helix bundle, respectively. The NT domain plays a critical role in binding to the low density lipoprotein receptor (LDLR), which eventually leads to lowering of plasma cholesterol levels. In order to be recognized by the LDLR, the helix bundle has to open and undergo a conformational change. The objective of the study was to understand the mechanism of opening of the helix bundle. Hydrogen/deuterium exchange mass spectrometry (HDX-MS) revealed that apoE3 NT domain adopts several disordered and unfolded regions, with H2 exhibiting relatively little protection against exchange-in compared to H1, H3, and H4. Site-directed fluorescence labeling indicated that H2 not only has the highest degree of solvent exposure but also the most flexibility in the helix bundle. It also indicated that the lipoprotein behavior of H1 was significnatly different from that of H2, H3 and H4. These results suggest that the opening of the helix bundle is likely initiated at the flexible end of H2 and the loop linking H2/H3, and involves movement of H2/H3 away from H1/H4. Together, these observations offer mechanistic insight

suggesting a regulated helix bundle opening of apoE3 NT domain can be triggered by lipid binding.

[31] *Jaacks LM, Sher S, Staercke C et al.* **Pilot randomized controlled trial of a Mediterranean diet or diet supplemented with fish oil, walnuts, and grape juice in overweight or obese US adults**. BMC nutrition 2018; 4:26.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30271610
ABSTRACT
Background: The 2015-2020 Dietary Guidelines for Americans recommend a Mediterranean-type diet as one of three healthful eating patterns. However, only one previous trial has evaluated the effects of a Mediterranean diet intervention in a US sample population. Methods: To address this gap, we conducted a pilot, non-blinded, 8-week randomized controlled trial on the comparative efficacy of consumption of a Mediterranean diet or a diet supplemented with fish oil, walnuts, and grape juice versus controls. Participants (overweight or obese US adults; 73% female and mean age 51 years) were randomly assigned to one of three groups: (1) Mediterranean diet; (2) habitual high-fat American-type diet supplemented with fish oil, walnuts, and grape juice; or (3) habitual high-fat American-type diet (controls). Intent-to-treat analysis of within-subject differences (Student's paired t-test or Wilcoxon sign ranks test) and between-subject differences (mixed-effects models with a group-by-time interaction term, adjusted for baseline health outcome) was conducted. Results: Participants in the Mediterranean diet arm (n = 11) had significantly greater weight loss despite no significant change in total caloric intake, and lower plasma cystine, indicative of decreased oxidative stress, compared to controls (n = 9) at both 4 and 8 weeks. Compared to controls, they also had significantly lower total cholesterol and low-density lipoprotein cholesterol levels at 4 weeks. Participants in the supplement arm (n = 10) had significantly lower adiponectin levels compared to controls at 4 weeks. No significant improvements in endothelial function or inflammatory biomarkers were observed in either intervention group compared to controls. Conclusion: These results suggest that adopting a dietary pattern reflecting a Mediterranean diet improves weight and cardio-metabolic health among overweight or obese US adults, and may be more beneficial than supplementing habitual American diets with fish oil, walnuts, and grape juice.

[32] *Aslibekyan S, Almasy L, Province MA et al.* **Data for GAW20: genome-wide DNA sequence variation and epigenome-wide DNA methylation before and after fenofibrate treatment in a family study of metabolic phenotypes**. BMC proceedings 2018; 12:35.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30275886
ABSTRACT
GAW20 provided participants with an opportunity to comprehensively examine genetic and epigenetic variation among related individuals in the context of drug treatment response. GAW20 used data from 188 families (N = 1105) participating in the Genetics of Lipid Lowering Drugs and Diet Network (GOLDN) study (clinicaltrials.gov identifier NCT00083369), which included CD4+ T-cell DNA methylation at 463,995 cytosine-phosphate-guanine (CpG) sites measured before and after a 3-week treatment with fenofibrate, single-nucleotide variation at 906,600 loci, metabolic syndrome components ascertained before and after the drug intervention, and relevant covariates. All GOLDN participants were of European descent, with

an average age of 48 years. In addition, approximately half were women and approximately 40% met the diagnostic criteria for metabolic syndrome. Unique advantages of the GAW20data set included longitudinal (3 weeks apart) measurements of DNA methylation, the opportunity to explore the contributions of both genotype and DNA methylation to the interindividual variability in drug treatment response, and the familial relationships between study participants. The principal disadvantage of GAW20/GOLDN data was the spurious correlation between batch effects and fenofibrate effects on methylation, which arose because the pre- and posttreatment methylation data were generated and normalized separately, and any attempts to remove time-dependent technical artifacts would also remove biologically meaningful changes brought on by fenofibrate. Despite this limitation, the GAW20 data set offered informative, multilayered omics data collected in a large population-based study of common disease traits, which resulted in creative approaches to integration and analysis of inherited human variation.

[33] *Cox JW, Patel D, Chung J et al.* **An efficient analytic approach in genome-wide identification of methylation quantitative trait loci response to fenofibrate treatment**. BMC proceedings 2018; 12:44.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30275893

ABSTRACT
Background: The study of DNA methylation quantitative trait loci (meQTLs) helps dissect regulatory mechanisms underlying genetic associations of human diseases. In this study, we conducted the first genome-wide examination of genetic drivers of methylation variation in response to a triglyceride-lowering treatment with fenofibrate (response-meQTL) by using an efficient analytic approach. Methods: Subjects (n = 429) from the GAW20 real data set with genotype and both pre- (visit 2) and post- (visit 4) fenofibrate treatment methylation measurements were included. Following the quality control steps of removing certain cytosine-phosphate-guanine (CpG) probes, the post-/premethylation changes (post/pre) were log transformed and the association was performed on 208,449 CpG sites. An additive linear mixed-effects model was used to test the association between each CpG probe and single nucleotide polymorphisms (SNPs) around +/-1 Mb region, with age, sex, smoke, batch effect, and principal components included as covariates. Bonferroni correction was applied to define the significance threshold (p < 5.6 x 10(- 10), given a total of 89,217,303 tests). Finally, we integrated our response-meQTL (re-meQTL) findings with the published genome-wide association study (GWAS) catalog of human diseases/traits. Results: We identified 1087 SNPs as cis re-meQTLs associated with 610 CpG probes/sites located in 351 unique gene loci. Among these 1087 cis re-meQTL SNPs, 229 were unique and 6 were co-localized at 8 unique disease/trait loci reported in the GWAS catalog (enrichment p = 1.51 x 10(- 23)). Specifically, a lipid SNP, rs10903129, located in intron regions of gene TMEM57, was a re-meQTL (p = 3.12 x 10(- 36)) associated with the CpG probe cg09222892, which is in the upstream region of the gene RHCE, indicating a new target gene for rs10903129. In addition, we found that SNP rs12710728 has a suggestive association with cg17097782 (p = 1.77 x 10(- 4)), and that this SNP is in high linkage disequilibrium (LD) (R(2) > 0.8) with rs7443270, which was previously reported to be associated with fenofibrate response (p = 5.00 x 10(- 6)). Conclusions: By using a novel analytic approach, we efficiently identified thousands of cis re-meQTLs that provide a unique

resource for further characterizing functional roles and gene targets of the SNPs that are most responsive to fenofibrate treatment. Our efficient analytic approach can be extended to large response quantitative trait locus studies with large sample sizes and multiple time points data.

[34] *Das S, Mondal PK, Ghosh S, Mukhopadhyay I*. **Family-based genome-wide association of inflammation biomarkers and fenofibrate treatment response in the GOLDN study**. BMC proceedings 2018; 12:41.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30275891
ABSTRACT
In this paper we analyzed whole-genome genetic information provided by GAW20 from the Genetics of Lipid Lowering Drugs and Diet Network (GOLDN) study for family data. Lipid levels such as triglycerides (TGs) and high-density lipoprotein (HDL) are measured at different time points before and after administration of an anti-inflammatory drug fenofibrate. Apart from that, the data contain some covariates and whole-genome genotype information. We propose 2 novel approaches based on Henderson's iterative mixed model to identify associated loci corresponding to (a) inflammatory biomarkers like TGs and HDLs together over time, and (b) the response to fenofibrate treatment. We developed a mixed-model approach using both TG and HDL phenotypes at all 4 time points for a genetic association study whereas we used TGs only to study genetic association with response to the drug. We expect that use of complete family data in a longitudinal framework under a single model involving the appropriate correlation structures would be able to exploit the maximum possible information contained in the sample. Our analysis of whole-genome single nucleotide polymorphisms (SNPs) and genomic regions corresponding to drug treatment finds no significant locus after multiple correction. Arguably, the moderately small sample size of the data set, as compared to the sample size usually used in genome-wide association studies (GWAS), could be a reason for such a result. Nevertheless, we report the top 20 SNPs associated with the phenotypes, and the top 20 SNPs and genomic regions associated with a response to fenofibrate treatment. Application of our methods to larger GWAS and further functional validation of the reported top SNPs and genomic regions might provide important biological insight into the genetic constitution of the trait.

[35] *Howey RAJ, Cordell HJ*. **Application of Bayesian networks to GAW20 genetic and blood lipid data**. BMC proceedings 2018; 12:19.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30275876
ABSTRACT
Background: Bayesian networks have been proposed as a way to identify possible causal relationships between measured variables based on their conditional dependencies and independencies. We explored the use of Bayesian network analyses applied to the GAW20 data to identify possible causal relationships between differential methylation of cytosine-phosphate-guanine dinucleotides (CpGs), single-nucleotide polymorphisms (SNPs), and blood lipid trait (triglycerides [TGs]). Methods: After initial exploratory linear regression analyses, 2 Bayesian networks analyses were performed. First, we used the real data and modeled the effects of 4 CpGs previously found to be associated with TGs in the Genetics of Lipid Lowering Drugs and Diet Network Study (GOLDN). Second, we used the simulated data and modeled the

effect of a fictional lipid modifying drug with 5 known causal SNPs and 5 corresponding CpGs. Results: In the real data we show that relationships are present between the CpGs, TGs, and other variables-age, sex, and center. In the simulated data, we show, using linear regression, that no CpGs and only 1 SNP were associated with a change in TG levels, and, using Bayesian network analysis, that relationships are present between the change in TG levels and most SNPs, but not with CpGs. Conclusions: Even when the causal relationships between variables are known, as with the simulated data, if the relationships are not strong then it is challenging to reproduce them in a Bayesian network.

[36] *Kraja AT, An P, Lenzini P et al.* **Simulation of a medication and methylation effects on triglycerides in the Genetic Analysis Workshop 20**. BMC proceedings 2018; 12:25.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30275880
ABSTRACT
The GAW20 simulation data set is based upon the companion Genetics of Lipid Lowering Drugs and Diet Network (GOLDN) study fenofibrate clinical trial data set that forms the real data example for GAW20. The simulated data problem consists of 200 simulated replications of what might happen if we were to repeat the GOLDN clinical trial 200 independent times, for these exact same subjects, but using a new fictitious drug (called "genomethate") that has a pharmaco-epigenetic effect on triglyceride response. For each replication, the pre-genomethate values at visits 1 and 2 are constant (ie, pedigree structures, age, sex, all phenotypes, covariates, genome-wide association study (GWAS) genotypes, and visit 2 methylation values), the same as the real GOLDN data across all 200 replications. Only the post-genomethate treatment data (ie, methylation and triglyceride levels for visits 3 and 4) change across the 200 replications. We postulate a growth curve pharmaco-epigenetic response model, in which each patient's response to genomethate treatment is individualized, and is dependent upon their genotype as well as the methylation state for key genes.

[37] *Lim E, Xu H, Wu P et al.* **Network analysis of drug effect on triglyceride-associated DNA methylation**. BMC proceedings 2018; 12:27.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30275881
ABSTRACT
Background: DNA methylation, an epigenetic modification, can be affected by environmental factors and thus regulate gene expression levels that can lead to alterations of certain phenotypes. Network analysis has been used successfully to discover gene sets that are expressed differently across multiple disease states and suggest possible pathways of disease progression. We applied this framework to compare DNA methylation levels before and after lipid-lowering medication and to identify modules that differ topologically between the two time points, revealing the association between lipid medication and these triglyceride-related methylation sites. Methods: We performed quality control using beta-mixture quantile normalization on 463,995 cytosine-phosphate-guanine (CpG) sites and deleted problematic sites, resulting in 423,004 probes. We identified 14,850 probes that were nominally associated with triglycerides prior to treatment and performed weighted gene correlation network analysis (WGCNA) to construct pre- and posttreatment methylation networks of these probes. We then applied both WGCNA module preservation and generalized Hamming distance (GHD)

to identify modules with topological differences between the pre- and posttreatment. For modules with structural changes between 2 time points, we performed pathway-enrichment analysis to gain further insight into the biological function of the genes from these modules. Results: Six triglyceride-associated modules were identified using pretreatment methylation probes. The same 3 modules were not preserved in posttreatment data using both the module-preservation and the GHD methods. Top-enriched pathways for the 3 differentially methylated modules are sphingolipid signaling pathway, proteoglycans in cancer, and metabolic pathways (p values < 0.005). One module in particular included an enrichment of lipid-related pathways among the top results. Conclusions: The same 3 modules, which were differentially methylated between pre- and posttreatment, were identified using both WGCNA module-preservation and GHD methods. Pathway analysis revealed that triglyceride-associated modules contain groups of genes that are involved in lipid signaling and metabolism. These 3 modules may provide insight into the effect of fenofibrate on changes in triglyceride levels and these methylation sites.

[38] *Nustad HE, Page CM, Reiner AH et al.* **A Bayesian mixed modeling approach for estimating heritability**. BMC proceedings 2018; 12:31.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30275883
ABSTRACT
Background: A Bayesian mixed model approach using integrated nested Laplace approximations (INLA) allows us to construct flexible models that can account for pedigree structure. Using these models, we estimate genome-wide patterns of DNA methylation heritability (h (2)), which are currently not well understood, as well as h (2) of blood lipid measurements. Methods: We included individuals from the Genetics of Lipid Lowering Drugs and Diet Network (GOLDN) study with Infinium 450 K cytosine-phosphate-guanine (CpG) methylation and blood lipid data pre- and posttreatment with fenofibrate in families with up to three-generation pedigrees. For genome-wide patterns, we constructed 1 model per CpG with methylation as the response variable, with a random effect to model kinship, and age and gender as fixed effects. Results: In total, 425,791 CpG sites pre-, but only 199,027 CpG sites posttreatment were found to have nonzero heritability. Across these CpG sites, the distributions of h (2) estimates are similar in pre- and posttreatment (pre: median = 0.31, interquartile range [IQR] = 0.16; post: median = 0.34, IQR = 0.20). Blood lipid h (2) estimates were similar pre- and posttreatment with overlapping 95% credibility intervals. Heritability was nonzero for treatment effect, that is, the difference between pre- and posttreatment blood lipids. Estimates for triglycerides h (2) are 0.48 (pre), 0.42 (post), and 0.21 (difference); likewise for high-density lipoprotein cholesterol h (2) the estimates are 0.61, 0.68, and 0.10. Conclusions: We show that with INLA, a fully Bayesian approach to estimate DNA methylation h (2) is possible on a genome-wide scale. This provides uncertainty assessment of the estimates, and allows us to perform model selection via deviance information criterion (DIC) to identify CpGs with strong evidence for nonzero heritability.

[39] *Yasmeen S, Burger P, Friedrichs S et al.* **Relating drug response to epigenetic and genetic markers using a region-based kernel score test**. BMC proceedings 2018; 12:47.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30275895

ABSTRACT
In GAW20, we investigated the association of specific genetic regions of interest (ROIs) with log-transformed triglyceride (TG) levels following lipid-lowering medication using epigenetic and genetic markers. The goal was to incorporate kernels for cytosine-phosphate-guanine (CpG) markers and compare the kernels to a purely parametric model. Post-treatment TG levels were investigated for post-methylation data at CpG sites and region-specific SNPs and adjusted for pre-treatment TG levels and age, in independent individuals only (real data: n = 150; simulated data, replicate 84: n = 111). In both data sets, our single-CpG-marker results using kernels and linear regression were in good agreement. In the real data, we investigated the introns of the CPT1A gene previously reported as associated with TG levels as separate ROIs, and were able to find hints of an association of cg17058475 and cg00574958 with post-treatment TG levels. In the simulated data, we investigated a total of 10 regions, in which the 5 causal and 5 non-causal markers lie, respectively, with increased methylation variances, yielding plausible results for the 3 window sizes. Overall, this indicates that kernels for CpG markers are feasible. An interaction regression model for the causal SNP with the nearest CpG marker identified an effect for the SNPs with the three greatest heritabilities simulated. The simulation model assumed full SNP effect only for unmethylated regions decreasing to zero in the case of full methylation. Thus, in the context of a clear candidate setting, interaction between epigenetic and genetic data may enhance information, albeit nominally, even with small sample sizes. Relieving the burden of multiple testing, developing kernels further to analyze data from multiple omics jointly is well warranted.

[40] *Cao YX, Li S, Liu HH, Li JJ*. **Impact of PCSK9 monoclonal antibodies on circulating hs-CRP levels: a systematic review and meta-analysis of randomised controlled trials**. BMJ open 2018; 8:e022348.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30287608

ABSTRACT
OBJECTIVE: To evaluate the potential effects of proprotein convertase subtilisin/kexin type 9 monoclonal antibody (PCSK9-mAb) on high-sensitivity C reactive protein (hs-CRP) concentrations. DESIGN: A systematic review and meta-analysis of randomised controlled trials. DATA SOURCES: PubMed, MEDLINE, the Cochrane Library databases, ClinicalTrials.gov and recent conferences were searched from inception to May 2018. ELIGIBILITY CRITERIA FOR SELECTING STUDIES: All randomised controlled trials that reported changes of hs-CRP were included. RESULTS: Ten studies involving 4198 participants were identified. PCSK9-mAbs showed a slight efficacy in reducing hs-CRP (-0.04 mg/L, 95% CI: -0.17 to 0.01) which was not statistically different. The results did not altered when subgroup analyses were performed including PCSK9-mAb types (alirocumab: 0.12 mg/L, 95% CI: -0.18 to 0.43; evolocumab: 0.00 mg/L, 95% CI: -0.07 to 0.07; LY3015014: -0.48 mg/L, 95% CI: -1.28 to 0.32; RG7652: 0.35 mg/L, 95% CI: -0.26 to 0.96), treatment duration (</=12w: 0.00 mg/L, 95% CI: -0.07 to 0.07; >12w: -0.11 mg/L, 95% CI: -0.45 to -0.23), participant characteristics (familial hypercholesterolaemia: 0.00 mg/L, 95% CI: -0.07 to 0.07; non-familial hypercholesterolaemia: 0.07 mg/L, 95% CI: -0.12 to 0.26; mix: -0.48 mg/L, 95% CI: -1.28 to 0.32) and treatment methods (monotherapy: 0.00 mg/L, -0.08 to 0.07; combination therapy: -0.08 mg/L, -0.37 to 0.21). Meta-regression analyses suggested no significant linear correlation between baseline age (p=0.673), sex (p=0.645) and

low-density lipoprotein cholesterol reduction (p=0.339). CONCLUSIONS: Our updated meta-analysis suggested that PCSK9-mAbs had no significant impact on circulating hs-CRP levels irrespective of PCSK9-mAb types, participant characteristics and treatment duration or methods.

[41] *Ren C, Li S, Liu K et al.* **Enhanced oxidative stress response and neuroprotection of combined limb remote ischemic conditioning and atorvastatin after transient ischemic stroke in rats**. Brain circulation 2017; 3:204-212.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30276326
ABSTRACT
BACKGROUND: Limb remote ischemic conditioning (LRIC) and atorvastatin (AtS) both provide neuroprotection in stroke. We evaluated the enhanced neuroprotective effect of combining these two treatments in preventing ischemia/reperfusion (I/R)-induced cerebral injury in a rat model and investigated the corresponding molecular mechanisms. MATERIALS AND METHODS: Transient cerebral ischemia was induced in Sprague-Dawley male rats by middle cerebral artery occlusion (MCAO) for 90 min followed by reperfusion (I/R). Rats were divided into 5 groups, sham, I/R, I/R + AtS, I/R + LRIC and I/R + AtS + LRIC. Pretreatment with LRIC and/or AtS for 14 days before MCAO surgery. Infarct volume, neurological score, Western blot, immuno-histochemical analyses were performed. RESULTS: The combination of LRIC plus AtS pretreatment decreased infarct volume and inhibited neuronal apoptosis. Combination treatment achieved stronger neuroprotection than monotherapy with LRIC or AtS. These therapies reduced reactive oxygen species production in the peri-ischemia region, associated with significantly increased expression and activation of superoxide dismutase 1, hemeoxygenase 1 and nuclear factor erythroid 2-related factor 2. CONCLUSIONS: Both LRIC and AtS + LRIC treatments conferred neuroprotection in ischemic stroke by reducing brain oxidative stress. AtS plus LRIC is an attractive translational research option due to its ease of use, tolerability, economical, and tremendous neuroprotective potential in stroke.

[42] *Iacocca MA, Wang J, Sarkar S et al.* **Whole-Gene Duplication of PCSK9 as a Novel Genetic Mechanism for Severe Familial Hypercholesterolemia**. The Canadian journal of cardiology 2018; 34:1316-1324.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30269829
ABSTRACT
BACKGROUND: Familial hypercholesterolemia (FH) is a common genetic disorder of severely elevated low-density lipoprotein (LDL) cholesterol, characterized by premature atherosclerotic cardiovascular disease. Although copy number variations (CNVs) are a large-scale mutation-type capable of explaining FH cases, they have been, to date, assessed only in the LDLR gene. Here, we performed novel CNV screening in additional FH-associated genes using a next-generation sequencing-based approach. METHODS: In 704 patients with FH, we sequenced FH-associated genes APOB, PCSK9, LDLRAP1, APOE, STAP1, LIPA, and ABCG5/8 using our LipidSeq targeted next-generation sequencing panel. Bioinformatic tools were applied to LipidSeq data for CNV screening, and identified CNVs were validated using whole-exome sequencing and microarray-based copy number analyses. RESULTS: We identified a whole-gene duplication of PCSK9 in 2 unrelated Canadian FH index cases; this PCSK9 CNV was also found to cosegregate

with affected status in family members. Features in affected individuals included severely elevated LDL cholesterol levels that were refractory to intensive statin therapy, pronounced clinical stigmata, premature cardiovascular events, and a plasma PCSK9 of approximately 5000 ng/mL in 1 index case. We found no CNVs in APOB, LDLRAP1, APOE, STAP1, LIPA, and ABCG5/8 in our cohort of 704 FH individuals. CONCLUSIONS: Here, we report the first description of a CNV affecting the PCSK9 gene in FH. This finding is associated with a profound FH phenotype and the highest known plasma PCSK9 level reported in a human. This finding also has therapeutic relevance, as elevated PCSK9 levels may limit the efficacy of high-dose statin therapy and also PCSK9 inhibition.

[43] *Mancini GBJ, Cheng AY, Connelly K et al.* **CardioDiabetes: Core Competencies for Cardiovascular Clinicians in a Rapidly Evolving Era of Type 2 Diabetes Management**. The Canadian journal of cardiology 2018; 34:1350-1361.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30269832
ABSTRACT
A sea change in the management of diabetes is occurring with the publication of clinical trials showing unequivocal cardiovascular (CV) protection through the use of certain antihyperglycemic agents. This change is similar to the change that occurred when lipid lowering with statins was first shown to have CV benefits, an event necessitating changes in training and the proactive treatment of lipids by CV specialists. As was the case then, many CV specialists currently feel poorly equipped to address diabetes with this new information even though diabetes is common in CV practice. The purpose of this overview is to provide an updated, comprehensive, and evidence-based CV protection plan for patients with type 2 diabetes, intended specifically for cardiologists and vascular medicine specialists. We attempt to elucidate a set of "CardioDiabetes" core competencies by merging the CV-relevant elements of the Diabetes Canada 2018 guidelines within a framework of comprehensive vascular protection as supported by other CV guidelines. We review the rationale for measuring hemoglobin A1C, understanding its use for establishing a diagnosis and for monitoring treatment. We also provide a brief review of the medications most important for a CV specialist to know. We provide useful memory aids and a succinct set of reminders and tips ("ABCDEFR'S") that can serve as a comprehensive checklist in the clinic and help to motivate trainees and clinicians to consult the original guideline source documents to enrich their knowledge and improve treatment in this rapidly changing arena.

[44] *Paquette M, Baass A*. **A Novel Cause of Familial Hypercholesterolemia: PCSK9 Gene Duplication**. The Canadian journal of cardiology 2018; 34:1259-1260.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30269825
ABSTRACT

[45] *Magri-Tomaz L, Melbouci L, Mercier J et al.* **Two weeks of high-fat feeding disturb lipid and cholesterol molecular markers**. Cell biochemistry and function 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30284312
ABSTRACT

Metabolic disorders are often associated with liver steatosis and increased plasma cholesterol levels. However, the link between excessive lipid accumulation and impairments in cholesterol metabolism remains uninvestigated in the liver. Short term of high-fat diet (HFD) was previously shown to promote excessive lipid accumulation prior to the development of metabolic disorders. The present study intended to characterize how increases in liver fat alter the expression of several key regulators of hepatic cholesterol metabolism in response to a short-term HFD. Wistar rats were randomly submitted either to HFD (n = 8) or a regular chow diet (n = 8) for 14 days. Increases in triglycerides were highly significant ($P < 0.01$) in the liver but marginal in the plasma of HFD rats. In contrast, the HFD resulted in higher ($P < 0.01$) cholesterol levels in plasma but not in liver samples. Gene expression of key markers involved in cholesterol uptake (LDL particles) including low-density lipoprotein receptor-related protein-1 (LRP-1) and protein convertase subtilisin/kexin type 9 (PCSK9) along with ATP-binding cassette, superfamily G, member 5 (ABCG5) involved in cholesterol exportation via bile ducts was found to be higher ($P < 0.05$) in response to the HFD. In contrast, expression of 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), involved in cholesterol synthesis, was downregulated in the liver. The data support the concept that excessive accumulation of lipids promptly alters the expression of key genes regulating cholesterol metabolism in the liver. On a clinical point of view, this indicates that increases in plasma cholesterol occur after a short-term HFD.

[46] *Husain I, Khan S, Khan S et al.* **Unfolding the pleiotropic facades of rosuvastatin in therapeutic intervention of myriads of neurodegenerative disorders**. Clinical and experimental pharmacology & physiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30290001
ABSTRACT
Rosuvastatin, a 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase inhibitor, and one of the most popular antihyperlipidemic medications has been found to possess pharmacodynamic activities much different from its usual indication. Recent research studies have revealed the efficacy of rosuvastatin in attenuating neuroinflammation, reducing the progression of Alzheimer's disease, providing protection against cerebral ischemia and spinal cord injury as well as ameliorating epilepsy. Mechanisms behind the neuroprotective potential of rosuvastatin can be attributed to its pleiotropic effects, independent of its ability to inhibit HMG-CoA reductase. These processes include modulation of several cellular pathways, isoprenylation, effects on oxidative stress, nitrosative levels, inflammation, and immune response. With this review, we aim to assimilate and summarize recent findings on the pharmacological actions of rosuvastatin in attenuating neurological disorders in order to give way for future research in this space. This article is protected by copyright. All rights reserved.

[47] *Liu Z, Lai CH, Zhang X et al.* **Simvastatin ameliorates total liver ischemia/reperfusion injury via KLF2-mediated mechanism in rats**. Clinics and research in hepatology and gastroenterology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30274910
ABSTRACT
OBJECTIVE: The total hepatic ischemia/reperfusion injury (IRI) involves the fact that both liver and gut are subjected to warm ischemia, which is a complex unavoidable process encountered

during liver transplantation and a serious threat to graft outcome. The ways to improve hepatic IRI are currently limited. The aim of the present study was to explore the protective effect of simvastatin on total hepatic IRI and examine the underlying mechanisms. METHODS: Male Sprague Dawley rats were subjected to total (100%) hepatic warm ischemia to induce hepatic IRI. Thirty-six male rats (250-300 g) were randomly divided into three groups: sham, IRI control and simvastatin (1 mg/kg) pretreatment 0.5 h before surgery. Serum samples and liver tissues were collected after reperfusion at 6 and 24 h for further studies. RESULTS: Simvastatin pretreatment significantly decreased the values of the transaminases alanine aminotransferase and aspartate aminotransferase and improved histological alterations according to improved Suzuki's Score ($P < 0.05$). Moreover, simvastatin upregulated the expression of Kruppel-like factor 2 (KLF2), phosphorylated endothelial nitric oxide synthase and thrombomodulin ($P < 0.05$). Furthermore, simvastatin pretreatment affected superoxide dismutase and malondialdehyde activities ($P < 0.05$) to reduce oxidative stress, and inhibited levels of high-mobility group box-1, CD68, toll-like receptor 4, tumor necrosis factor alpha, interleukin-1beta and interleukin-6 ($P < 0.05$) to suppress inflammatory response. CONCLUSION: Simvastatin pretreatment ameliorates total hepatic IRI via a KLF2-mediated protective mechanism. Simvastatin may be used as a potential prophylactic treatment strategy for clinical trials against hepatic IRI.

[48] *Tai MH, Shepherd J, Bailey H et al.* **Real-world treatment patterns of PCSK9 inhibitors among patients with dyslipidemia in Germany, Spain, and United Kingdom**. Current medical research and opinion 2018:1-17.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30289004
ABSTRACT
OBJECTIVE: Proprotein convertase subtilisin/kexin type 9 antibody inhibitors (PCSK9i) are approved as adjuncts to maximal tolerated statin therapy to lower low-density lipoprotein cholesterol (LDL-C). This study describes real-world use, characteristics of PCSK9i users and non-users, and factors influencing treatment choice. METHODS: A physician and patient survey was conducted in Germany, Spain, and United Kingdom (UK) from December 2016 to April 2017 through the Adelphi Dyslipidemia Disease Specific Programme. Physicians reported patients' lipid-lowering therapy (LLT) history and characteristics. PSCK9i users were systematically over-sampled. Results were summarized using frequencies and proportions. RESULTS: The study included 110, 123, and 117 physicians from Germany, Spain, and UK, respectively, providing data on 3,073 patients (mean age: 62 years; 60% male). Most patients (63% - 73%) had prior statin and/or ezetimibe use. Compared to patients receiving other LLT (N = 2,686), PCSK9i users (222 Germany, 97 Spain, 68 UK) were, on average, 5 - 7.5 years younger and had LDL-C at diagnosis averaging 23 - 53 mg/dl higher. Familial hypercholesterolemia (FH), coronary heart/artery disease, myocardial infarction and acute coronary syndrome were more common among PCSK9i users than non-users. PCSK9i users were also more likely to use high-intensity statins in their current LLT regimen (64% - 89% versus 28% - 50%). Physicians commonly reported PCSK9i benefits on LDL-C and total cholesterol as reasons for initiating these agents, and PCSK9i users reported good knowledge of cardiovascular disease and treatment options. CONCLUSIONS: Results indicate that physicians are prescribing PCSK9i to patients with high cardiovascular risk in accordance with European guidelines and reimbursement requirements.

[49] *Meyer D, Merkel M*. **[Hyperlipidemia: What role do PCSK9 inhibitors play?]**. Deutsche medizinische Wochenschrift (1946) 2018; 143:1430-1434.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30286489
ABSTRACT
PCSK9 inhibitors are a new and safe option of lowering LDL cholesterol. This article summarizes current recommendations for the use of PCSK9 inhibitors. Statins and ezetimibe are still the basis of cholesterol-lowering therapy. Through their use, the largest proportion of patients can be adequately treated. PCSK9 inhibitors should be used in patients at very high cardiovascular risk if, despite the maximum tolerated statin/ezetimibe therapy, an LDL-C reduction of more than 50 % would be needed to achieve the recommended LDL-C target. The use in patients with familial hypercholesterolemia is usually carried out according to this scheme as well. For statin intolerance, PCSK9 inhibitors should be considered in patients at very high cardiovascular risk who have not tolerated low doses of at least two different statins/ezetimibe.

[50] *Ghasemi A, Ghashghai Z, Akbari J et al.* **Topical atorvastatin 1% for prevention of skin toxicity in patients receiving radiation therapy for breast cancer: a randomized, double-blind, placebo-controlled trial**. Eur J Clin Pharmacol 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30291370
ABSTRACT
BACKGROUND AND PURPOSE: The purpose of this randomized, placebo-controlled, double-blind study was to investigate the preventive effect of topical administration of atorvastatin (ATV) on the acute radiation-induced skin toxicity in patients with breast cancer. PATIENTS AND METHODS: Seventy breast cancer patients were randomly assigned to use topical ATV 1% or placebo gels during radiotherapy twice daily. Radiation-induced dermatitis was classified according to the radiation therapy oncology group (RTOG) criteria, as well as pain and itching were scored according to VAS (visual analogue scale) for 6 weeks of treatment. RESULTS: Topical administration of ATV gel during radiotherapy reduced significantly radiation-induced breast swelling, itching, and pain in breast cancer patients by factors of 1.8, 1.7, and 1.5, respectively. ATV reduced the redness caused by radiotherapy in patients as compared with placebo; however, this difference was statistically not significant. CONCLUSION: ATV was able to reduce significantly itching, breast edema, and pain in patients during radiotherapy.

[51] *Li HY, Liu F, Gao C, Wang HR*. **Protective effect of simvastatin on arterial plaque instability induced by p-cresyl sulfate**. European review for medical and pharmacological sciences 2018; 22:6149-6155.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30280803
ABSTRACT
OBJECTIVE: To study the protective effect of simvastatin on arterial plaque instability induced by p-cresyl sulfate (PCS). MATERIALS AND METHODS: Apolipoprotein E (ApoE)-/- mice were selected as objects of this study. All mice were randomly divided into three groups: 1) the control group, 2) the PCS group and 3) the PCS + simvastatin group. After successful modeling, the levels of plasma cholesterol, triglyceride, low-density lipoprotein, high-density lipoprotein, interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor-beta (TNF-beta) were

detected. The gross specimen of coronary artery was stained. Meanwhile, oil red O staining and Sirius red staining were performed for coronary arterial sections to observe the lipid and collagen components. The expression levels of smooth muscle cells and macrophages were observed by immunohistochemistry. In addition, the expression levels of matrix metalloproteinases (MMPs), tissue inhibitors of metalloproteinases (TIMPs) and monocyte chemoattractant protein-1 (MCP-1) in tissues were detected by Western blotting. RESULTS: Simvastatin could improve atherosclerotic plaque growth and atherosclerotic plaque instability induced by PCS. Moreover, simvastatin could also improve the changes of MMPs and TIMPs caused by PCS as well as the inflammatory status in mice. CONCLUSIONS: Simvastatin can improve the inflammatory status in mice, eventually improving the arterial plaque instability caused by PCS.

[52] *Qian XS, Song JX, Zhu MH*. **Correlation between adiponectin polymorphism and atherosclerotic plaque compositions under intravascular ultrasound (IVUS)**. European review for medical and pharmacological sciences 2018; 22:6100-6108.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30280797
ABSTRACT
OBJECTIVE: To discuss the correlation between polymorphism of rs266729 (-11377C/G, Cytosine/Guanine) (adiponectin promoter) site and atherosclerotic plaque compositions as well as related indicators under intravascular ultrasound (IVUS). PATIENTS AND METHODS: 76 patients with coronary heart disease from December 2014 to December 2016 were enrolled. The PCR-RFLP method was used to analyze the adiponectin gene polymorphism in rs266729 site. All the objects were divided into CC type group (n=26), CG type group (n=23), and GG type group (n=27) according to the results of polymorphism. The amount of lesions and length of lesion in the vessel were determined according to the images of coronary angiography. The indicators from each group, including minimum external elastic membrane area, the smallest lumen area, the patch area, the patch load, the lipid pool area, the lipid pool/plaque area, the fiber cap thickness, the reconstruction index, the positive reconstruction, the negative reconstruction and the patch character were measured according to the IVUS results. RESULTS: The baseline data from distinct the gene types showed no significant difference. The results of quantitative IVUS plaque analysis indicated a statistical difference of factors such as plaque area, plaque burden, lipid pool area, lipid pool/plaque area, and remodeling index between the CC and GG types ($p<0.05$). The levels of aminopeptidase N (APN), tumor necrosis factor alpha (TNF-alpha), interleukin 1 beta (IL-1beta), fasting serum insulin (FIN), triglyceride (TG), and low-density lipoprotein cholesterol (LDL-C) among diverse groups presented statistical difference ($p<0.05$). Of note, the analysis results of IVUS qualitative components of plaque showed that soft plaque in CC group was 42.3% (11/26), which was significantly lower than GG group 11.1% (3/27) ($p<0.05$). The vascular remodeling ratio in CC group 26.9% (7/26) was also significantly decreased compared to that in GG group 66.7% (18/27) ($p<0.05$). The tubular and diffuse ratio in CC groups according to the comparison of diseased vessel, count, length of the lesion were 34.6% (9/26) and 42.3% (11/26), respectively. CONCLUSIONS: Our data on biochemical indicators demonstrates CC type gives rise to poor prognosis compared to GG type does, which suggests that close attention should be paid in the impact of adiponectin polymorphism on atherosclerotic plaque compositions.

[53] *Iughetti L, Predieri B, Bruzzi P, Balli F*. **Approaches to dyslipidemia treatment in children and adolescents**. Expert review of endocrinology & metabolism 2008; 3:615-633.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30290407
ABSTRACT
Atherosclerosis represents a disease that begins in childhood, and alterations in lipid concentration play a fundamental role in the development of this condition. Children and adolescents with high cholesterol levels are more likely than their peers in the general population to present with dyslipidemia in adulthood. Precocious identification of dyslipidemias associated with premature cardiovascular disease is crucial during childhood to delay or prevent the atherosclerotic process. The National Cholesterol Education Program has established guidelines for the diagnosis and treatment of dyslipidemia during pediatric age. It has been suggested that a heart-healthy diet should begin at 2 years of age, and no adverse effects on psychological aspects, growth, pubertal development and nutritional status in children and adolescents limiting total and saturated fat intake have been demonstrated. Pharmacotherapy should be considered in children aged 10 years or older when low-density lipoprotein cholesterol concentrations remain very high despite dietary therapy, especially when multiple risk factors are present. The lipid-lowering drugs recommended for childhood and adolescence are resins and statins. The increasing use of statins is dependent on their effectiveness and safety. Ezetimibe, a selective cholesterol absorption inhibitor, may provide a similar cholesterol-lowering effect as that reached with statin treatment. This review provides an update on recent advances in the therapy of dyslipidemia, especially hypercholesterolemia, during pediatric age and adolescence.

[54] *Otterbeck PE, Banerji MA*. **The efficacy and safety of vildagliptin in the GALIANT trial: chronic kidney disease and other applications**. Expert review of endocrinology & metabolism 2011; 6:143-151.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30290444
ABSTRACT
The number of mechanistically novel antidiabetes agents has dramatically increased over the past few years. Dipeptidyl peptidase-4 (DPP-4) inhibitors in particular have emerged as clinically efficacious oral agents for diabetes management with a low incidence of side effects. The Galvus in Addition to Metformin versus Tzd/Metformin in Lowering HbA1c (GALIANT) trial showed that vildagliptin as an add-on therapy was noninferior to thiazolidinedione therapy with regard to reduction in hemoglobin A1c, with both drugs having a similar incidence of side effects in patients with normal and impaired renal function. DPP-4 inhibitors have a low incidence of hypoglycemia without significant weight gain and there is strong evidence that the administration of vildagliptin results in improved alpha- and beta-cell function. New data suggest that DPP-4 inhibitors might also have a role in the setting of myocardial infarction and lipid management, and in the prevention of Type 2 diabetes.

[55] *Alver M, Palover M, Saar A et al.* **Recall by genotype and cascade screening for familial hypercholesterolemia in a population-based biobank from Estonia**. Genetics in medicine : official journal of the American College of Medical Genetics 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30270359

ABSTRACT

PURPOSE: Large-scale, population-based biobanks integrating health records and genomic profiles may provide a platform to identify individuals with disease-predisposing genetic variants. Here, we recall probands carrying familial hypercholesterolemia (FH)-associated variants, perform cascade screening of family members, and describe health outcomes affected by such a strategy. METHODS: The Estonian Biobank of Estonian Genome Center, University of Tartu, comprises 52,274 individuals. Among 4776 participants with exome or genome sequences, we identified 27 individuals who carried FH-associated variants in the LDLR, APOB, or PCSK9 genes. Cascade screening of 64 family members identified an additional 20 carriers of FH-associated variants. RESULTS: Via genetic counseling and clinical management of carriers, we were able to reclassify 51% of the study participants from having previously established nonspecific hypercholesterolemia to having FH and identify 32% who were completely unaware of harboring a high-risk disease-associated genetic variant. Imaging-based risk stratification targeted 86% of the variant carriers for statin treatment recommendations. CONCLUSION: Genotype-guided recall of probands and subsequent cascade screening for familial hypercholesterolemia is feasible within a population-based biobank and may facilitate more appropriate clinical management.

[56] *Shahab O, Biswas R, Paik J et al.* **Among Patients With NAFLD, Treatment of Dyslipidemia Does Not Reduce Cardiovascular Mortality**. Hepatology communications 2018; 2:1227-1234.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30288477

ABSTRACT

Dyslipidemia is one of the common risk factors for NAFLD and is associated with cardiovascular (CV) mortality, which is the most common cause of death in NAFLD. Lipid-lowering agents (LLAs) are used to reduce CV events in the general population. Our aim was to assess whether the use of LLAs in patients with NAFLD can reduce the risk of CV mortality. We used the third National Health and Nutrition Examination Survey mortality linked files. Mortality was determined from the National Death Index records through 2011. NAFLD was diagnosed by ultrasound after exclusion of other causes of liver disease. After inclusion and exclusion, the cohort consisted of 2,566 patients with NAFLD (45.8% < 45 years of age, 52.8% male, 75.4% white). Those who were taking LLAs were more likely to be older, non-Hispanic white, and had significantly higher rates of diabetes mellitus (DM), hyperlipidemia, hypertension, metabolic syndrome, and history of CV disease (CVD) (all P< 0.01). In our multivariate analysis, DM was an independent predictor of overall mortality (adjusted hazard ratio [aHR]: 1.79 [95% confidence interval (CI): 1.40-2.30]) and CV mortality (aHR: 1.89 [95% CI: 1.08-3.30]). History of CVD was associated with both overall (aHR: 2.03 [95% CI: 1.57-2.63]) and CV mortality (aHR: 3.69 [95% CI: 2.23-6.08]). In contrast, the use of statins and other LLAs was not associated with reduction in overall (aHR = 0.95 [95% CI: 0.37-2.44] and aHR = 1.43 [95% CI: 0.99-2.07]) and CV mortality (aHR = 1.20 [95% CI: 0.26-5.54] and aHR = 1.63 [95% CI: 0.70-3.76]). Conclusion: The use of statins and other LLAs did not reduce the increased risk of overall or CV mortality in NAFLD.

[57] *Goncalves RSG, Dantas AT, Pereira MC et al.* **Statins Inhibit Cytokines in a Dose-Dependent Response in Patients with Systemic Sclerosis**. Inflammation 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30288636

ABSTRACT

Although statins have been successfully administered in the treatment of hypercholesterolemia and cardiovascular disease due to their lipid-lowering and anti-atherosclerotic action, they have shown immunomodulatory effects in several studies with immune-mediated diseases. The aim of this study was to investigate the effects of statins treatment on Th1, Th2, and Th17 cytokines production from stimulated peripheral blood mononuclear cells (PBMCs) obtained from Systemic Sclerosis (SSc) patients. We recruited 21 patients classified according to the American College of Rheumatology criteria for SSc for PBMCs culture analysis. Cytokine levels (IL-2, IL-4, IL-6, IL-10, TNF, IFN-gamma, IL-17A, and IL-17F) were quantified by ELISA or CBA, and patients were assessed for clinical and exam's variables. Simvastatin and atorvastatin at 50 muM promoted reduction in all cytokine levels with statistical significance, except for IL-6, which had its reduction only induced by the use of simvastatin. Statins, particularly simvastatin, appear to have an immunosuppressive effect in reducing all cytokine secretion levels from PBMCs of SSc in a dose-dependent manner.

[58] *Bronzato S, Durante A*. **Dietary Supplements and Cardiovascular Diseases**. International journal of preventive medicine 2018; 9:80.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30283612

ABSTRACT

The market of nutritional supplements is expected to expand over 6%/year through 2018 due to growing interest in personal health, aging population, and promising personalized care products. The most used dietary supplements are fish oil, multivitamins, Vitamin D, and coenzyme Q10 (CoQ10) in this order, while probiotics is the fastest growing supplement. In the U.S., over 68% of the population use dietary supplements regularly. On the other hand, in the developed countries, cardiovascular diseases (CVDs) are the main cause of death and morbidity from the 1900s. The effects of most dietary supplements on cardiovascular risk and CVD have been studied for a long time. However, despite several studies explored the association of the various supplements to the cardiovascular risk, there is still a lack of consensus. Multivitamin supplementation has been advocated to reduce cardiovascular events; Vitamin D levels have been associated with the occurrence of coronary artery disease, heart failure, and atrial fibrillation; CoQ10 deficiency has been associated with myocardial dysfunction and with statin myopathy; probiotoics has been suggested to lower both blood pressure and circulating lipids. However, the study of the effects of dietary supplementations is not straightforward, since people assuming dietary supplements generally have a healthier diet and lifestyle, and randomized studies are rarely performed. In this review, we will summarize the findings linking dietary supplements to CVD with a special focus on novel insights.

[59] *Sawami K, Tanaka A, Nakamura T et al.* **Multiple potency of ezetimibe in a patient with macroproteinuric chronic kidney disease and statin-intolerant dyslipidemia**. Journal of cardiology cases 2018; 17:204-207.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30279893

ABSTRACT

Dyslipidemia is often complicated by chronic kidney disease (CKD). Lipid-lowering medications may be effective, in part, for inhibiting development and progression of CKD. Ezetimibe, a cholesterol absorption inhibitor, has pleiotropic actions, including anti-inflammatory and anti-oxidant effects, contributing to a decreased risk of cardiovascular diseases. A 40-year-old woman was admitted with dyslipidemia and macroproteinuria, whose samples of renal biopsy showed exudative lesions, but without glomerular basement membrane thickening or nodular lesions, in some glomeruli. Blood glycemic parameters were normal. After initiation of atorvastatin, she developed muscle pain and an increase in serum creatine kinase. Twelve months after switching to ezetimibe, serum levels of low-density lipoprotein cholesterol and triglyceride reduced from 170 mg/dL to 116 mg/dL and from 320 mg/dL to 160 mg/dL, respectively. Although serum creatinine levels remained unchanged after 12 months, urinary protein excretion and urinary liver-type fatty acid binding protein were reduced. Flow-mediated dilatation also increased from 4.9% to 5.5% after 12 months, associated with a slight decrease in mean intima-media thickness in the common carotid artery from 0.722 mm to 0.718 mm. These results suggest that ezetimibe protects against renal and vascular damage in patients with CKD and statin-intolerant dyslipidemia. <Learning objective: Little is known whether ezetimibe monotherapy is safe and effective for renal/vascular function in patients with chronic kidney disease (CKD). We report that ezetimibe monotherapy for 12 months improved lipid profiles in a patient with CKD and statin-intolerant dyslipidemia. Ezetimibe also reduced proteinuria and urinary liver-type fatty acid binding protein levels, improved endothelial function, and decreased carotid atherosclerosis. These findings suggest that ezetimibe monotherapy may have beneficial multipotent effects on renal/vascular function.>.

[60] *Zdybel M, Chodurek E, Pilawa B*. **Effect of simvastatin in different concentrations on free radicals in A-2058 human melanoma malignum cells-EPR studies**. Journal of cellular biochemistry 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30277600
ABSTRACT
The influence of concentration of simvastatin (SIM) on free radicals in A-2058 human melanoma malignum cells was studied. The proliferation assay for melanoma A-2058 cells with SIM in concentration range from 0.1 to 20 microM was performed. SIM in the concentrations of 0.1, 0.3, and 1 muM only slightly changed the growth of A-2058 cells, but the growth of the cells considerably decreased for higher concentrations of SIM. Free radicals in the cells were examined by an X-band (9.3 GHz) electron paramagnetic resonance (EPR) spectroscopy. o-Semiquinone free radicals with g-factors in the range of 2.0060 to 2.0065 were found in A-2058 cells. The asymmetric broad EPR spectra with linewidths (DeltaBpp) from 0.87 to 1.25 mT were measured. The fast spin-lattice relaxation processes characterized all the tested cells. The free radical concentrations in the all A-2058 cells cultured with SIM were lower than in the control cells. The quenching of free radicals in A-2058 cells depended on concentration of SIM. This effect was the weakest for concentration of SIM of 3 muM. The strongest decrease of free radical concentration caused SIM in concentration of 1 muM.

Literature update week 40 (2018)

[61] *Nakano T, Inoue I, Takenaka Y et al.* **Luminal plant sterol promotes brush border membrane-to-lumen cholesterol efflux in the small intestine**. Journal of clinical biochemistry and nutrition 2018; 63:102-105.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30279620
ABSTRACT
Plant sterols are used as food additives to reduce intestinal cholesterol absorption. They also increase fecal neutral sterol (FNS) excretion irrespective of the absorption inhibition. Intestine-mediated reverse cholesterol transport, or trans-intestinal cholesterol efflux (TICE), provides the major part of the increase of FNS excretion. However, it is unknown whether plant sterols stimulate TICE or not. We have shown previously that TICE can be evaluated by brush border membrane (BBM)-to-lumen cholesterol efflux. Thus, we examined whether luminal plant sterols stimulate BBM-to-lumen cholesterol efflux in the intestinal tract or not in mice. Cannulated upper jejunum that had been pre-labeled with orally given (3)H-cholesterol, was flushed and perfused to collect (3)H-cholesterol effluxed back into the lumen from the BBM to estimate the efflux efficiency. Adding 0.5 mg/ml of plant sterols, but not cholesterol, in the perfusion solution doubled the efflux. Plant sterols enter the BBM and are effluxed back to the lumen rapidly, in which process cholesterol transporters in the BBM are involved. We thus speculate that phytosterols alter cholesterol flux in the BBM; thereby, increases BBM-to-lumen cholesterol efflux, resulting in the increased TICE.

[62] *Zitnanova I, Siarnik P, Fullop M et al.* **Gender differences in LDL- and HDL-cholesterol subfractions in patients after the acute ischemic stroke and their association with oxidative stress markers**. Journal of clinical biochemistry and nutrition 2018; 63:144-148.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30279626
ABSTRACT
The aim of our study was to examine gender differences of LDL- and HDL-cholesterol subfractions in patients after the acute ischemic stroke with focus on small LDL and HDL subfractions, and their association with oxidative stress markers. In addition, we have monitored the 7-day effect of cholesterol-lowering drugs administered to patients after the acute ischemic stroke, on these subfractions. Eighty two stroke patients and 81 age matched controls were included in this study. Blood was collected from patients within 24 h after the stroke (group A) and re-examined at the 7-day follow-up (group B). We have found gender differences in LDL- and HDL-subfractions in stroke patients, lipid-lowering drugs administered to acute ischemic stroke patients significantly reduced all measured parameters of lipoprotein profile. In the group A LDL1 subfraction positively correlated with activity of antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase) indicating a protective role of this subfraction. On the contrary, small HDL subfractions positively correlated with lipoperoxide levels and negatively with trolox equivalent antioxidant capacity in plasma suggesting a negative role of these subfractions. In this work we have confirmed the hypothesis of atherogenic properties of small HDL subfractions and anti-atherogenic properties of large LDL1-subfractions.

Literature update week 40 (2018)

[63] *Hovingh GK, Guyton JR, Langslet G et al.* **Alirocumab dosing patterns during 40 months of open-label treatment in patients with heterozygous familial hypercholesterolemia**. Journal of clinical lipidology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30287210
ABSTRACT
BACKGROUND: ODYSSEY OLE (NCT01954394) was an open-label extension (OLE) study for patients with heterozygous familial hypercholesterolemia (HeFH) who had completed previous phase 3 clinical trials with alirocumab. Alirocumab dose could be increased or decreased as per physician judgment. OBJECTIVE: To assess how the alirocumab dosing strategy was used by physicians during OLE. METHODS: Patients who entered OLE on a starting dose of alirocumab 75 mg every 2 weeks (Q2W) were included in the analysis (those from FH I, FH II, and LONG TERM trials). Those who completed LONG TERM entered an 8-week washout period before receiving alirocumab 75 mg Q2W at the start of OLE. From week 12, dose adjustment from 75 to 150 mg Q2W, or vice versa, was possible, based on the physician's clinical judgment. RESULTS: In total, 909 patients with HeFH completed the 3 parent studies and were treated during OLE for a duration of up to 40 months. Most patients (56.7%) were maintained on 75 mg Q2W throughout OLE, whereas 43.3% of patients had their dose increased to 150 mg Q2W. The dose was subsequently decreased in 7.4% of the patients in whom alirocumab was initially uptitrated. Overall, treatment-emergent adverse events were similar between those who had received placebo or alirocumab in the parent studies. CONCLUSIONS: In the opinion of physicians, alirocumab 75 mg Q2W enabled over half of patients with HeFH to achieve sufficient low-density lipoprotein cholesterol lowering.

[64] *Larsen S, Vigelso A, Dandanell S et al.* **Simvastatin-Induced Insulin Resistance May Be Linked to Decreased Lipid Uptake and Lipid Synthesis in Human Skeletal Muscle: the LIFESTAT Study**. Journal of diabetes research 2018; 2018:9257874.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30276217
ABSTRACT
Background: A prevalent side-effect of simvastatin is attenuated glucose homeostasis. The underlying mechanism is unknown, but impaired lipid metabolism may provide the link. The aim of this study was to investigate whether simvastatin-treated patients had a lower capacity to oxidize lipids and reduced expression of the major proteins regulating lipid uptake, synthesis, lipolysis, and storage in skeletal muscle than matched controls. Materials and Methods: Ten men were treated with simvastatin (HbA1c: 5.7 +/- 0.1%), and 10 healthy men (HbA1c: 5.2 +/- 0.1%) underwent an oral glucose tolerance test and a muscle biopsy was obtained. Fat oxidation rates were measured at rest and during exercise. Western blotting was used to assess protein content. Results: Patients treated with simvastatin had impaired glucose tolerance compared with control subjects, but fat oxidation at rest and during exercise was compatible. Skeletal muscle protein content of CD36, lipoprotein lipase (LPL), and diacylglycerol acyltransferase (DGAT) 1 were lower, and DGAT 2 tended to be lower in patients treated with simvastatin. Conclusions: Patients treated with simvastatin had a reduced capacity to synthesize FA and diacylglycerol (DAG) into triacylglycerol in skeletal muscle compared to matched controls. Decreased lipid synthesis capacity may lead to accumulation of lipotoxic intermediates (FA and DAG) and hence impair glucose tolerance.

[65] *Sarsam S, Berry A, Degheim G et al.* **Real-world use of PCSK9 inhibitors: A single-center experience**. J Int Med Res 2018:300060518800595.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30280628
ABSTRACT
Objective Hyperlipidemia is an important risk factor for atherosclerotic cardiovascular disease. Many patients are intolerant to or have limited benefit from statins. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have been approved for treating hyperlipidemia in these patients. We sought to investigate the impact of these medications in a real-world cardiology practice. Methods This was a retrospective study of 17 patients with either heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease with low-density lipoprotein cholesterol (LDL-C) levels above the treatment target despite maximally tolerated statins. Baseline lipid profile was compared with a repeat lipid profile obtained 4 to 6 weeks after initiating treatment with a PCSK9 inhibitor. Results The average duration of PCSK9 inhibitor treatment was 10.7 months. Lipid profile comparison showed that total cholesterol decreased from 243 +/- 72 to 148 +/- 39 (mg/dL) (39% reduction), triglycerides decreased from 185 +/- 86 to 149 +/- 62 (mg/dL) (19.5% reduction), high-density lipoprotein cholesterol increased from 56 +/- 20 to 62 +/- 26 (mg/dL) (10.7% increase), and LDL-C decreased from 154 +/- 30 to 57 +/- 32 (mg/dL) (63% reduction) from baseline. Conclusions PCSK9 inhibitors as add-on therapy to maximally tolerated statins resulted in an approximately 63% reduction in LDL-C.

[66] *Valanti EK, Dalakoura-Karagkouni K, Sanoudou D*. **Current and Emerging Reconstituted HDL-apoA-I and HDL-apoE Approaches to Treat Atherosclerosis**. Journal of personalized medicine 2018; 8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30282955
ABSTRACT
Atherosclerosis affects millions of people worldwide. However, the wide variety of limitations in the current therapeutic options leaves much to be desired in future lipid-lowering therapies. For example, although statins, which are the first-line treatment for coronary heart disease (CHD), reduce the risk of cardiovascular events in a large percentage of patients, they lead to optimal levels of low density lipoprotein-cholesterol (LDL-C) in only about one-third of patients. A new promising research direction against atherosclerosis aims to improve lipoprotein metabolism. Novel therapeutic approaches are being developed to increase the levels of functional high density lipoprotein (HDL) particles. This review aims to highlight the atheroprotective potential of the in vitro synthesized reconstituted HDL particles containing apolipoprotein E (apoE) as their sole apolipoprotein component (rHDL-apoE). For this purpose, we provide: (1) a summary of the atheroprotective properties of native plasma HDL and its apolipoprotein components, apolipoprotein A-I (apoA-I) and apoE; (2) an overview of the anti-atherogenic functions of rHDL-apoA-I and apoA-I-containing HDL, i.e., natural HDL isolated from transgenic Apoa1(-/-) x Apoe(-/-) mice overexpressing human apoA-I (HDL-apoA-I); and (3) the latest developments and therapeutic potential of HDL-apoE and rHDL-apoE. Novel rHDL formulations containing apoE could possibly present enhanced biological functions, leading to improved therapeutic efficacy against atherosclerosis.

[67] *Wahlin B, Innala L, Magnusson S et al.* **Performance of the Expanded Cardiovascular Risk Prediction Score for Rheumatoid Arthritis Is Not Superior to the ACC/AHA Risk Calculator**. The Journal of rheumatology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30275258
ABSTRACT
OBJECTIVE: Cardiovascular (CV) risk estimation calculators for the general population do not perform well in patients with rheumatoid arthritis (RA). An RA-specific risk calculator has been developed, but did not perform better than a risk calculator for the general population when validated in a heterogeneous multinational cohort. METHODS: In a cohort of patients with new-onset RA from northern Sweden (n = 665), the risk of CV disease was estimated by the Expanded Cardiovascular Risk Prediction Score for Rheumatoid Arthritis (ERS-RA) and the American College of Cardiology/American Heart Association algorithm (ACC/AHA). The ACC/AHA estimation was analyzed, both as crude data and when adjusted according to the recommendations by the European League Against Rheumatism (ACC/AHA x 1.5). ERS-RA was calculated using 2 variants: 1 from patient and physician reports of hypertension (HTN) and hyperlipidemia [ERS-RA (reported)] and 1 from assessments of blood pressure (BP) and blood lipids [ERS-RA (measured)]. The estimations were compared with observed CV events. RESULTS: All variants of risk calculators underestimated the CV risk. Discrimination was good for all risk calculators studied. Performance of all risk calculators was poorer in patients with a high grade of inflammation, whereas ACC/AHA x 1.5 performed best in the high-inflammatory patients. In those patients with an estimated risk of 5-15%, no risk calculator performed well. CONCLUSION: ERS-RA underestimated the risk of a CV event in our cohort of patients, especially when risk estimations were based on patient or physician reports of HTN and hyperlipidemia instead of assessment of BP and blood lipids. The performance of ERS-RA was no better than that of ACC/AHA x 1.5, and neither performed well in high-inflammatory patients.

[68] *Guntekin U, Tosun V, Kilinc AY et al.* **ST segment elevation myocardial infarction (STEMI) patients are more likely to achieve lipid-lowering treatment goals: A retrospective analysis of patients presenting with first acute coronary syndromes**. Medicine (Baltimore) 2018; 97:e12225.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30278492
ABSTRACT
Statin nonadherence or discontinuation is associated with increased cardiovascular events. Many factors related to the physicians or the patients are influential in this. We aimed to compare the compliance with statin therapy between the patients who first presented with ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), and unstable angina pectoris (UA) based on the target achievement according to the current dyslipidemia guidelines.We retrospectively acquired all the information about demographic characteristics, in-hospital revascularization procedures, prescribed treatments, and index and up to 6-month follow-up laboratory results of the first acute coronary syndrome patients. Acute coronary syndrome patients were divided into 3 groups as STEMI, NSTEMI, and UA.The STEMI group consisted of 260 patients, NSTEMI group consisted of 560 patients, and UA group consisted of 206 patients. Seventy-six percent of patients underwent percutaneous coronary

interventions, 18.3% were managed medically, and 5.7% were referred for coronary artery bypass grafting. There was a significant decrease in low-density lipoprotein-cholesterol (LDL-C) values with the statin treatment at the follow-up in all 3 groups (for all P < .001). In the STEMI group, the percentage of those achieving the target LDL-C level was significantly higher than those who did not achieve the target according to both The American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology dyslipidemia guidelines. The LDL-C target achievement rates were also higher in the STEMI group than in the NSTEMI and UA groups.Our study concluded that statin treatment goals were more attained in STEMI patients than NSTEMI and UA. All physicians should encourage lifelong intensive statin treatment in UA and NSTEMI patients such as STEMI patients.

[69] *Klarin D, Damrauer SM, Cho K et al.* **Genetics of blood lipids among ~300,000 multi-ethnic participants of the Million Veteran Program**. Nature genetics 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30275531
ABSTRACT
The Million Veteran Program (MVP) was established in 2011 as a national research initiative to determine how genetic variation influences the health of US military veterans. Here we genotyped 312,571 MVP participants using a custom biobank array and linked the genetic data to laboratory and clinical phenotypes extracted from electronic health records covering a median of 10.0 years of follow-up. Among 297,626 veterans with at least one blood lipid measurement, including 57,332 black and 24,743 Hispanic participants, we tested up to around 32 million variants for association with lipid levels and identified 118 novel genome-wide significant loci after meta-analysis with data from the Global Lipids Genetics Consortium (total n > 600,000). Through a focus on mutations predicted to result in a loss of gene function and a phenome-wide association study, we propose novel indications for pharmaceutical inhibitors targeting PCSK9 (abdominal aortic aneurysm), ANGPTL4 (type 2 diabetes) and PDE3B (triglycerides and coronary disease).

[70] *Howe PRC, Evans HM, Kuszewski JC, Wong RHX*. **Effects of Long Chain Omega-3 Polyunsaturated Fatty Acids on Brain Function in Mildly Hypertensive Older Adults**. Nutrients 2018; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30279397
ABSTRACT
Purported benefits of long chain omega-3 polyunsaturated fatty acid (LCn-3PUFA) for brain function may be attributable, at least in part, to improved cerebral perfusion. A pilot randomised controlled trial was undertaken to investigate effects of taking a DHA-rich fish oil supplement for 20 weeks on cerebrovascular function, mood and cognitive performance. Borderline hypertensives aged 40(-)85 years with low habitual LCn-3PUFA intake took four capsules/day of EPAX (1600 mg DHA + 400 mg EPA) or placebo (corn oil). Cerebrovascular function was assessed at baseline and after 20 weeks in 38 completers (19 on each supplement) using transcranial Doppler ultrasound of blood flow in the middle cerebral artery at rest and whilst performing a battery of cognitive tasks (neurovascular coupling). The primary outcome, cerebrovascular responsiveness (CVR) to hypercapnia, increased 26% (p = 0.024) in women; there was no change in men. In contrast, neurovascular coupling increased significantly (p =

0.01 for the overall response) in men only; the latter correlated with an increase of EPA in erythrocytes (r = 0.616, p = 0.002). There was no associated improvement of mood or cognition in either men or women. These preliminary observations indicate that LCn-3PUFA supplementation has the potential to enhance blood flow in the brain in response to both hypercapnic and cognitive stimuli. Future studies should examine differential effects of EPA and DHA and take account of the gender differences in responsiveness to supplementation.

[71] *Simental-Mendia LE, Guerrero-Romero F*. **Effect of resveratrol supplementation on lipid profile in subjects with dyslipidemia: A randomized double-blind, placebo-controlled trial**. Nutrition 2018; 58:7-10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30278430
ABSTRACT
OBJECTIVES: The aim of this study was to explore the effect of resveratrol supplementation on lipid profile in individuals with dyslipidemia. METHODS: Apparently healthy men and non-pregnant women 20 to 65 y of age with new diagnosis of dyslipidemia were enrolled in a randomized double-blind, placebo-controlled trial and randomly allocated to receive either resveratrol 100mg/d or placebo (sucrose 0.5 g/d) for 2 mo. Smoking, alcohol intake, diabetes, acute or chronic renal or hepatic diseases, malignancy, cardiovascular disease, serum triacylglycerol levels >/=400mg/dL, low-density lipoprotein cholesterol levels >/=190mg/dL, and consumption of lipid-lowering drugs or supplements containing resveratrol were exclusion criteria. RESULTS: Seventy-one individuals with new diagnosis of dyslipidemia were enrolled and randomly allocated to the resveratrol (n=35) or placebo groups (n=36). At baseline, there were no significant differences between the study groups. After intervention period, individuals in the resveratrol group showed a significant decrease in total cholesterol (201.4 +/- 34.4 versus 220.6 +/- 37.4, P=0.04) and triacylglycerol (133.4 +/- 55.3 versus 166.7 +/- 68.5, P=0.04) concentrations compared with the placebo group, without significant statistical differences for high-density lipoprotein cholesterol and low-density lipoprotein cholesterol levels. CONCLUSION: The results suggest that resveratrol supplementation significantly reduces total cholesterol and triacylglycerol concentrations in individuals with dyslipidemia.

[72] *Alexander W*. **European Society of Cardiology Congress 2018**. P & T : a peer-reviewed journal for formulary management 2018; 43:622-626.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30271107
ABSTRACT
We review sessions on large-scale aspirin and anticoagulation trials, weight loss therapies, fish oil, gout, endocarditis, and cardiomyopathy, with important implications for health care providers.

[73] *Hadi A, Pourmasoumi M, Najafgholizadeh A et al.* **Effect of purslane on blood lipids and glucose: A systematic review and meta-analysis of randomized controlled trials**. Phytotherapy research : PTR 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30281177
ABSTRACT

Despite a history of purslane usage as a herbal treatment for dyslipidemia and hyperglycemia management, existing evidence from clinical trials is controversial. The aim for the current study was to evaluate the efficacy of purslane supplementation on lipid parameters and glycemic status in adult populations. A systematic review was conducted in PubMed, Scopus, ISI Web of Science, and Google Scholar up to January 15, 2018, searching for randomized controlled trials that assessed the impact of purslane on fasting blood glucose (FBG), triglycerides, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C). Based on the detected heterogeneity between studies, a random- or fixed-effect model was applied in the meta-analysis. The findings from six randomized controlled trials, comprising 352 participants, indicated that purslane can reduce FBG (-4.54 mg/dl, 95% CI [-7.54, -1.53]; I(2) = 0.53%) and triglycerides (-19.16 mg/dl, 95% CI [-38.17, -0.15]; I(2) = 0%) levels. Changes in TC, LDL-C, and HDL-C concentrations did not reach a statistically significant level. Subgroup analysis showed a favorable effects of purslane on FBG, triglycerides, TC, and LDL-C in a subset of studies in which purslane was administered >1.5 g/day. Categorization based on gender showed that purslane was more effective in improving FBG, TC and LDL-C in females compared with males. This systematic review and meta-analysis suggested that the purslane might be effective on the improvement of blood lipid and glucose levels. Further robust studies with sufficient durations and dosages of supplementation are needed to confirm these results.

[74] *Manichaikul A, Wang XQ, Li L et al.* **Lp-PLA2, scavenger receptor class B type I gene (SCARB1) rs10846744 variant, and cardiovascular disease**. PloS one 2018; 13:e0204352.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30289950

ABSTRACT

BACKGROUND: We previously reported association of SCARB1 SNP rs10846744 with common carotid IMT (cIMT) and cardiovascular disease (CVD) events. Since rs10846744 has been reported in association with Lp-PLA2 mass and activity, we hypothesized that inflammatory pathways might mediate the association of rs10846744 with atherosclerosis. METHODS: We first examined association of rs10846744 in CVD in multiple large-scale consortium-based genome-wide association studies. We further examined 27 parameters of interest, including Lp-PLA2 mass and activity, inflammatory markers, and plasma phospholipid fatty acids, and fatty acid ratios in participants from the Multi-Ethnic Study of Atherosclerosis (MESA), as potential mediators in the pathway linking rs10846744 with cIMT and incident CVD. Finally, we examined the association of rs10846744 with Lp-PLA2 activity, cardiovascular outcomes, and interaction with the Lp-PLA2 inhibitor, darapladib, in the Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy (STABILITY) and Stabilization of Plaque using Darapladib-Thrombolysis in Myocardial Infarction 52 (SOLID-TIMI 52) studies. RESULTS: SCARB1 rs10846744 was associated with coronary artery disease events in CARDIoGRAMplusC4D (odds ratio 1.05; 95% CI [1.02, 1.07]; P = 1.4x10-4). In combined analysis across race/ethnic groups in MESA, rs10846744 was associated with Lp-PLA2 mass (P = 0.04) and activity (P = 0.001), homocysteine (P = 0.03), LDL particle number (P = 0.01), docosahexaenoic acid [DHA] (P = 0.01), docosapentaenoic acid [DPA] (P = 0.04), DPA/ eicosapentaenoic acid [EPA] ratio (P = 0.002), and DHA/EPA ratio (P = 0.008). Lp-PLA2 activity was identified as a mediator of rs10846744 with cIMT in a basic model (P = 8x10-5), but not after adjustment for CVD risk factors. There was no

interaction or modifier effect of the Lp-PLA2 inhibitor darapladib assignment on the relationship between rs10846744 and major CVD events in either STABILITY or SOLID-TIMI 52. SUMMARY: SCARB1 rs10846744 is significantly associated with Lp-PLA2 activity, atherosclerosis, and CVD events, but Lp-PLA2 activity is not a mediator in the association of rs10846744 with cIMT in MESA.

[75] *Woo Y, Shin JS, Shim CY et al.* **Effect of fenofibrate in 1113 patients at low-density lipoprotein cholesterol goal but high triglyceride levels: Real-world results and factors associated with triglyceride reduction**. PloS one 2018; 13:e0205006.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30286170
ABSTRACT
Fibrates are used in patients with dyslipidemia and high cardiovascular risk. However, information regarding drug response to fibrate has been highly limited. We investigated treatment results and factors associated with triglyceride reduction after fenofibrate therapy using large-scale real-world data. Patients with one or more cardiovascular risk factors, at low-density lipoprotein-cholesterol goal but with triglyceride level >/=150 mg/dL, and undergoing treatment with fenofibrate 135-160 mg for the first time were included in this retrospective observational study. The outcome variable was the percentage changes of TG levels. The achievement rate of triglyceride <150 mg/dL was additionally analyzed. Factors associated with treatment results were also analyzed. Among 2546 patients who were initially screened, 1113 patients were enrolled (median age: 61 years; male: 71%). After median follow-up of 4 months, the median change in triglyceride was -60%, and 49% of the patients reached triglyceride <150 mg/dL. After adjusting for confounding variables, female sex, non-diabetic status, coronary artery disease, lower baseline triglyceride, and no statin use were identified to be independently associated with achievement of triglyceride <150 mg/dL. Among them, female sex, non-diabetic status, and coronary artery disease were also related to median or greater percentage reduction of triglyceride. In conclusion, only half of the study patients reached triglyceride levels <150 mg/dL after real-world fenofibrate therapy. This study indicates that more attention is needed on some subgroups to obtain optimal triglyceride levels when treating with fenofibrate.

[76] *Farnier M*. **[New guidelines on dyslipidemia management]**. Presse medicale (Paris, France : 1983) 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30274915
ABSTRACT
Total cardiovascular risk estimation using a system such as SCORE is recommended for adults>40years of age without evidence of cardiovascular disease, diabetes, chronic kidney disease, severe hypertension or familial hypercholesterolemia. Before treatment, a full lipid profile is recommended, fasting in French guidelines, fasting or non-fasting in European guidelines. LDL-C has to be used as the primary target for treatment. For patients with elevated triglycerides, non-HDL-C level is also recommended as the secondary goal for treatment. In patients at very high and high cardiovascular risk, LDL-C goals are respectively below<0.70g/L and<1.0g/L. For subjects at very high and high cardiovascular risk, French guidelines do not mention that a>/=50% reduction in LDL-C should be achieved. Statins are the treatment of

choice to reach LDL-C goals. If the goal is not reached on maximally tolerated dose of statin, combination with another LDL lowering drug, mainly ezetimibe, is recommended. Fibrates are mainly proposed for patients with severe hypertriglyceridemia (TG>5g/L after lifestyle changes).

[77] *Hamzeh M, Hosseinimehr SJ, Khalatbary AR et al.* **Atorvastatin mitigates cyclophosphamide-induced hepatotoxicity via suppression of oxidative stress and apoptosis in rat model**. Research in pharmaceutical sciences 2018; 13:440-449.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30271446
ABSTRACT
Cyclophosphamide (CP), as a chemotherapy drug, induces hepatotoxicity through causing oxidative stress. Atorvastatin (ATV) at a low dose has antioxidant and anti-inflammatory properties. The present study was designed to investigate the protective effects of ATV against CP-induced hepatotoxicity in rat. In this experimental study, 32 rats were treated with ATV orally at a dose of 10 mg/kg for 10 consecutive days, 5 days before and 5 days after the administration of a single intraperitoneal injection of CP (150 mg/kg). The hepatoprotective effect of ATV was evaluated by measuring liver function markers, oxidative markers, histological and immunohistochemical assays. The biochemical results showed that administration of CP increased hepatic biomarkers enzymes as aspartate aminotransferase (AST), alanine aminotransferase (ALT) and lactate dehydrogenase (LDH) levels. CP increased malondialdehyde (MDA), protein carbonyl (PC) and decreased glutathione (GSH) content in rats. Moreover, administration of CP was associated with periportal leucocyte infiltration, dilation sinusoids, hepatocyte vacuolation, congestion and hemorrhage in livers of rats. CP significantly increased immunoreactivity of caspase-3 as a marker of apoptosis in liver tissue. ATV markedly mitigated liver injury through reduction in oxidative stress biomarkers, histopathological findings and apoptosis. The antioxidant and anti-apoptotic activities of ATV are main proposed mechanisms involved in its hepatoprotective effects against CP-induced hepatic injury.

[78] *Bagge A, Schott U, Kander T*. **High-dose omega-3 fatty acids have no effect on platelet aggregation or coagulation measured with static and flow-based aggregation instruments and Sonoclot; an observational study in healthy volunteers**. Scandinavian journal of clinical and laboratory investigation 2018:1-7.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30270671
ABSTRACT
The effect of omega-3 fatty acids on platelet aggregation and coagulation is highly unclear. Studies both support and refute the impacts of omega-3 fatty acids on prolonged bleeding time and platelet inhibition as well as its purported positive effects on cardiovascular disease. In a previous pilot study we suggested an inhibition of platelet aggregation measured with multiple electrode aggregometry. Following on that, the aim of the present study was to investigate the effects of supplementary high doses of omega-3 fatty acids on platelet aggregation and coagulation in a sample-size calculated number of healthy volunteers using Sonoclot, multiple electrode aggregometry, and flow-based Cellix instruments after 10 days of omega-3 fatty acid intake. Twelve healthy human volunteers ingested 2520 mg of supplementary omega-3 fatty acids per day for 10 days. Venous blood was sampled and platelet aggregation and coagulation were measured before and after the treatment period. The viscoelastic test instrument

Sonoclot, multiple electrode aggregometry, and flow-based Cellix instruments with collagen-coated channels were used to evaluate platelet aggregation and coagulation. There were no differences in any of the measured variables after the treatment period as compared to before. In this well-powered study on healthy volunteers, no effects of high doses of omega-3 fatty acids after 10 days of intake could be demonstrated, either on coagulation or platelet function. Further studies are needed to clarify whether omega-3 fatty acids have a role in the regulation of the putative complex processes in vivo.

[79] *Han JS, Kim K, Jung Y et al.* **Metabolic Alterations Associated with Atorvastatin/Fenofibric Acid Combination in Patients with Atherogenic Dyslipidaemia: A Randomized Trial for Comparison with Escalated-Dose Atorvastatin**. Scientific reports 2018; 8:14642.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30279504
ABSTRACT
In the current study, the metabolic effects of atorvastatin dose escalation versus atorvastatin/fenofibric acid combination were compared using metabolomics analyses. Men and women with combined hyperlipidaemia were initially prescribed atorvastatin (10 mg, >/=4 weeks). Patients who reached low-density lipoprotein-cholesterol targets, but had triglyceride and high-density lipoprotein-cholesterol levels >/=150 mg/dL and <50 mg/dL, respectively, were randomized to receive atorvastatin 20 mg or atorvastatin 10 mg/fenofibric acid 135 mg for 12 weeks. Metabolite profiling of serum was performed and changes in metabolites after drug treatment in the two groups were compared. Analysis was performed using patients' samples obtained before and after treatment. Of 89 screened patients, 37 who met the inclusion criteria were randomized, and 34 completed the study. Unlike that in the dose-escalation group, distinct clustering of both lipid and aqueous metabolites was observed in the combination group after treatment. Most lipid metabolites of acylglycerols and many of ceramides decreased, while many of sphingomyelins increased in the combination group. Atorvastatin dose escalation modestly decreased lysophosphatidylcholines; however, the effect of combination therapy was variable. Most aqueous metabolites decreased, while L-carnitine remarkably increased in the combination group. In conclusion, the atorvastatin/fenofibric acid combination induced distinct metabolite clustering. Our results provide comprehensive information regarding metabolic changes beyond conventional lipid profiles for this combination therapy.

[80] *Nezic L, Skrbic R, Amidzic L et al.* **Simvastatin Protects Cardiomyocytes Against Endotoxin-induced Apoptosis and Up-regulates Survivin/NF-kappaB/p65 Expression**. Scientific reports 2018; 8:14652.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30279549
ABSTRACT
This study is aimed to investigate whether simvastatin induces cardiomyocytes survival signaling in endotoxin (lipopolysaccharide, LSP)-induced myocardial injury, and if so, further to determine a role of survivin in simvastatin-anti-apoptotic effect. Wistar rats were pretreated with simvastatin (10-40 mg/kg po) before a single non-lethal dose of LPS. In myocardial tissue, LPS induced structural disorganization of myofibrils with significant inflammatory infiltrate (cardiac damage score, CDS = 3.87 +/- 0.51, $p < 0.05$), whereas simvastatin dose-dependently

abolished structural changes induced by LPS ($p < 0.01$). Simvastatin in 20 mg/kg and 40 mg/kg pretreatment, dose dependently, attenuated myocardial apoptosis determined as apoptotic index (28.8 +/- 4.5% and 18.9 +/- 3.5, $p < 0.05$), decreased cleaved caspase-3 expression (32.1 +/- 5.8%, $p < 0.01$), along with significant Bcl-xL expression in the simvastatin groups ($p < 0.01$). Interestingly, in the simvastatin groups were determined significantly increased expression of survivin ($p < 0.01$), but in negative correlation with cleaved caspase-3 and apoptotic indices ($p < 0.01$). Simvastatin has a cardioprotective effects against LPS induced apoptosis. The effect may be mediated by up-regulation of survivin via activation of NF-kappaB, which leads to reduced activation of caspase-3 and consequent apoptosis of cardiomyocytes in experimental sepsis.

[81] *Nunez-Garcia M, Gomez-Santos B, Saenz de Urturi D et al.* **Atorvastatin provides a new lipidome improving early regeneration after partial hepatectomy in osteopontin deficient mice**. Scientific reports 2018; 8:14626.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30279550
ABSTRACT
Osteopontin (OPN), a multifunctional cytokine that controls liver glycerolipid metabolism, is involved in activation and proliferation of several liver cell types during regeneration, a condition of high metabolic demands. Here we investigated the role of OPN in modulating the liver lipidome during regeneration after partial-hepatectomy (PH) and the impact that atorvastatin treatment has over regeneration in OPN knockout (KO) mice. The results showed that OPN deficiency leads to remodeling of phosphatidylcholine and triacylglycerol (TG) species primarily during the first 24 h after PH, with minimal effects on regeneration. Changes in the quiescent liver lipidome in OPN-KO mice included TG enrichment with linoleic acid and were associated with higher lysosome TG-hydrolase activity that maintained 24 h after PH but increased in WT mice. OPN-KO mice showed increased beta-oxidation 24 h after PH with less body weight loss. In OPN-KO mice, atorvastatin treatment induced changes in the lipidome 24 h after PH and improved liver regeneration while no effect was observed 48 h post-PH. These results suggest that increased dietary-lipid uptake in OPN-KO mice provides the metabolic precursors required for regeneration 24 h and 48 h after PH. However, atorvastatin treatment offers a new metabolic program that improves early regeneration when OPN is deficient.

[82] *Irwin JC, Fenning AS, Ryan KR, Vella RK*. **Validation of a clinically-relevant rodent model of statin-associated muscle symptoms for use in pharmacological studies**. Toxicology and applied pharmacology 2018; 360:78-87.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30268577
ABSTRACT
Various rodent models of statin-associated muscle symptoms (SAMS) have been used to investigate the aetiology of statin myotoxicity. Variability between these models, however, may be contributing to the ambiguity currently surrounding the pathogenesis of SAMS. Furthermore, few studies have assessed the reproducibility of these models. The aim of this study was to compare two established rodent models of statin myotoxicity, differing in treatment duration and dose, to determine which reproducibly caused changes characteristic of SAMS. Isolated skeletal muscle organ bath experiments, biochemical analyses, real-time quantitative-PCR and biometric assessments were used to compare changes in skeletal muscle

and renal integrity in statin-treated animals and time-matched control groups. The SIM80 model (80mgkg(-1)day(-1) simvastatin for 14days) produced fibre-selective skeletal muscle damage characteristic of SAMS. Indeed, fast-twitch gastrocnemius muscles showed increased Atrogin-1 expression, reduced peak force of contraction and decreased Myh2 expression while slow-twitch soleus muscles were unaffected. Contrastingly, the SIM50 model (50mgkg(-1)day(-1) simvastatin for 30days) produced little evidence of significant skeletal muscle damage. Neither statin treatment protocol caused significant pathological changes to the kidney. The results of this study indicate that the SIM80 model induces a type of SAMS in rodents that resembles the presentation of statin-induced myalgia in humans. The findings support that the SIM80 model is reproducible and can thus be reliably used as a platform to assess the aetiology and treatment of this condition.

[83] *Ferreira L, Palma I, Bacelar C et al.* **Lipoprotein apheresis in the management of severe hypercholesterolemia and hyperlipoproteinemia(a)-The Portuguese experience**. Transfusion and apheresis science : official journal of the World Apheresis Association : official journal of the European Society for Haemapheresis 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30287070
ABSTRACT
BACKGROUND: Low-density lipoprotein cholesterol (LDL-C) and lipoprotein(a) (Lp(a)) are established causal risk factors for cardiovascular disease (CVD). Lipoprotein apheresis is often required for treatment of patients with a high risk for CVD due to hypercholesterolemia and/or hyperlipoproteinemia(a). AIM: To describe our experience with lipoprotein apheresis in patients with severe hypercholesterolemia or with hyperlipoproteinemia(a). METHODS: We retrospectively investigated patients treated with Lipoprotein apheresis using direct adsorption of lipoproteins (DALI) technique, between December 2008 and March 2018, in our center. Adverse events, acute and long term reductions in lipid parameters were analyzed. RESULTS: Between December 2008 and March 2018, a total of 950 treatments were performed in five patients, four with heterozygous familial hypercholesterolemia (HeFH), all on maximally tolerated cholesterol-lowering drug therapy and in one patient with hyperlipoproteinemia(a) and progressive CVD. In the four patients with HeFH we obtained mean acute reductions in LDL-C and non-high-density lipoprotein cholesterol (non-HDL-C) of 62.0 +/- 7.8% and 60.4 +/- 6.8%, respectively. Regarding long-term efficacy we achieved a mean reduction of 43.1% in LDL-C and of 41.2% in non-HDL-C. In the patient with hyperlipoproteinemia(a) we attained mean acute reductions of 60.4 +/- 6.4% in Lp(a) and of 75.4 +/- 7.3% in LDL-C per session and long term reductions in Lp(a) and LDL-C of 67.4% and 40.5%, respectively. Adverse events were recorded in only 1.2% of treatments. CONCLUSION: Lipoprotein apheresis is an efficient and safe treatment in severely hypercholesterolemic patients who are refractory to conservative lipid-lowering therapy or with hyperlipoproteinemia(a) and progressive CVD.

[84] *Roder ME, Hildebrandt P, Storgaard H, Heitmann M*. **[Cholesterol-lowering treatment with PCSK9-inhibitors]**. Ugeskrift for laeger 2018; 180.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30274588
ABSTRACT

Monoclonal antibodies inhibiting proprotein convertase subtilisin-kexin type 9 constitute a new class of lipid-lowering drugs. Currently, evolocumab and alirocumab are marketed. A recent cardiovascular outcome study with evolocumab has shown a cardiovascular (CV) event reduction of 15% in high-risk individuals at very low levels of low-density lipoproteins. The adverse event profile up to two years is mild. Treatment is very costly, and data on CV endpoints are still limited. Treatment is restricted to patients at very high risk of getting CV diseases and on a maximal tolerated statin and ezetimibe treatment in addition to dietary intervention.

[85] *Nomura S, Taniura T, Shouzu A et al.* **Effects of sarpogrelate, eicosapentaenoic acid and pitavastatin on arterioslcerosis obliterans-related biomarkers in patients with type 2 diabetes (SAREPITASO study)**. Vascular health and risk management 2018; 14:225-232.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30271161

ABSTRACT

Background: The aim was to evaluate the significance of arteriosclerosis obliterans-related biomarkers in patients with type 2 diabetes mellitus (T2DM), and to compare the effects of sarpogrelate, eicosapentaenoic acid (EPA) and pitavastatin on these markers. Patients and methods: Seventy-two arteriosclerosis obliterans patients with T2DM were classified into two groups, pitavastatin with either sarpogrelate (PS) or EPA (PE). We observed no differences in all biomarkers between the PS and PE groups before treatments. Results: The levels of body mass index, hemoglobin A1c, soluble E-selectin, soluble vascular cell adhesion molecule 1, plasminogen activator inhibitor-1 and platelet-derived microparticle in the PE group decreased significantly after treatment. The ankle branchial pressure index and adiponectin levels significantly increased in the PE group after treatment compared with the PS group. Conclusion: These results suggest that combination therapy using pitavastatin and EPA possesses an antiatherosclerotic effect and may be beneficial for prevention of vascular complications in patients with T2DM.