Literature update week 04 (2018)

[1] *Greve AM, Bang CN, Boman K et al.* **Effect Modifications of Lipid-Lowering Therapy on Progression of Aortic Stenosis (from the Simvastatin and Ezetimibe in Aortic Stenosis [SEAS] Study)**. The American journal of cardiology 2017.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29361285
ABSTRACT
Observational studies indicate that low-density lipoprotein (LDL) cholesterol acts as a primary contributor to an active process leading to aortic stenosis (AS) development. However, randomized clinical trials have failed to demonstrate an effect of lipid lowering on impeding AS progression. This study explored if pretreatment LDL levels and AS severity altered the efficacy of lipid-lowering therapy. The study goal was evaluated in the analysis of surviving patients with baseline data in the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial of 1,873 asymptomatic patients with mild-to-moderate AS. Serially measured peak aortic jet velocity was the primary effect estimate. Linear mixed model analysis adjusted by baseline peak jet velocity and pretreatment LDL levels was used to assess effect modifications of treatment. Data were available in 1,579 (84%) patients. In adjusted analyses, lower baseline peak aortic jet velocity and higher pretreatment LDL levels increased the effect of randomized treatment (p = 0.04 for interaction). As such, treatment impeded progression of AS in the highest quartile of LDL among patients with mild AS at baseline (0.06 m/s per year slower progression vs placebo in peak aortic jet velocity, 95% confidence interval 0.01 to 0.11, p = 0.03), but not in the 3 other quartiles of LDL. Conversely, among patients with moderate AS, there was no detectable effect of treatment in any of the pretreatment LDL quartiles (all p >/=0.14). In conclusion, in a non-prespecified post hoc analysis, the efficacy of lipid-lowering therapy on impeding AS progression increased with higher pretreatment LDL and lower peak aortic jet velocity (SEAS study: NCT00092677).

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PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29365462
ABSTRACT

[3] *Alyavi A, Alyavi B, Uzokov J*. **Efficiency and safety of rosuvastatin in patients with metabolic syndrome**. Atherosclerosis 2017; 263:e245.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29365938
ABSTRACT

[4] *Askri I, Kelbousi S, Sakly M, Attia N*. **Atorvastatin effect on phospholipid profile and distribution between lipoprotein fractions in type 2 diabetic patients with and without CAD**. Atherosclerosis 2017; 263:e246.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29365941
ABSTRACT

[5] *Balzarotti G, Tibolla G, Ruscica M et al.* **Role of PCSK9 (proprotein convertase subtilisin/kexin type 9) beyond LDLR targeting: Focus on glucose metabolism**. Atherosclerosis 2017; 263:e102.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29365433
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[6] *Baragetti A, Garlaschelli K, Grigore L et al.* **Differential contribution of PCSK9 and LPL gene variants on lipid profile in the general population**. Atherosclerosis 2017; 263:e66.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29366186
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[7] *Barale C, Bonomo K, Noto F et al.* **Effects of PCSK9 inhibitors on platelet function in adults with hypercholesterolemia**. Atherosclerosis 2017; 263:e30-e31.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29366074
ABSTRACT

[8] *Baudin B, Nekaies Y, Baudin B et al.* **Association of apolipoproteins plasma levels with PCSK9 in type 2 diabetes mellitus**. Atherosclerosis 2017; 263:e273-e274.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29366032
ABSTRACT

[9] *Benimetskaya K, Ragino Y, Shakhtshneider E et al.* **Proprotein convertase subtilisin/kexin type 9 (PCSK9) level in patients with familial hypercholesterolemia in Russia**. Atherosclerosis 2017; 263:e195.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29365754
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PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29365860
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PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29365650
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[12] *Capisizu A, Aurelian SM, Paun AM et al.* **Effects of lipid lowering therapy with statins on cognitive functions in patients diagnosed with dementia undergoing antidementive therapy**. Atherosclerosis 2017; 263:e238.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29365916
ABSTRACT

[13] *Cariou B, Courtemanche H, Le May C et al.* **PCSK9 cerebrospinal fluid concentrations are not increased in Alzheimer's disease**. Atherosclerosis 2017; 263:e104.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29365439
ABSTRACT

[14] *Casula M, Scotti L, Bernocchi O et al.* **Ldl-cholesterol reduction with PCSK9 inhibitors: A meta-analysis of randomised controlled trials**. Atherosclerosis 2017; 263:e244.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29365936
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[15] *Cegla J, Walji S, Jones B, Scott J*. **PCSK9 inhibition: "real world" experience from the hammersmith hospital lipid clinic, London**. Atherosclerosis 2017; 263:e244-e245.
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[16] *Cicero A, Ruscica M, Ferri N et al.* **Circulating levels of PCSK9 and arterial stiffness in a large population sample: Data from the brisighella heart study**. Atherosclerosis 2017; 263:e105-e106.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29365441
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[17] *Cocci G, Cenci A, Bordicchia M, Sarzani R*. **LDLR, PCSK9, and LDLRAP1 mutations in the same patient in a familial hypercholesterolemia (FH) family**. Atherosclerosis 2017; 263:e232.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29365898
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PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29366106
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PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29365969
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[26] *Gonzalez Molero I, Olveira G, Tinahones F*. **Features of first patients treated with PCSK9 inhibitors in a specific lipid unit and effectiveness on lipid profile in familial hypercholesterolemia**. Atherosclerosis 2017; 263:e239.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29365920
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PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29365915
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PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29365913
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PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29365937
ABSTRACT

[32] *Hilvo M, Simolin H, Metso J et al.* **PCSK9 inhibition alters the lipidome of plasma and lipoprotein fractions**. Atherosclerosis 2018; 269:159-165.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29366988
ABSTRACT
BACKGROUND AND AIMS: While inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9) is known to result in dramatic lowering of LDL-cholesterol (LDL-C), it is poorly understood how it affects other lipid species and their metabolism. The aim of this study was to characterize the alterations in the lipidome of plasma and lipoprotein particles after administration of PCSK9 inhibiting antibody to patients with established coronary heart disease. METHODS: Plasma samples were obtained from patients undergoing a randomized placebo-controlled phase II trial (EQUATOR) for the safe and effective use of RG7652, a fully human monoclonal antibody inhibiting PCSK9 function. Lipoprotein fractions were isolated by sequential density ultracentrifugation, and both plasma and major lipoprotein classes (VLDL-IDL, LDL, HDL) were subjected to mass spectrometric lipidomic profiling. RESULTS: PCSK9 inhibition significantly decreased plasma levels of several lipid classes, including sphingolipids (dihydroceramides, glucosylceramides, sphingomyelins, ceramides), cholesteryl esters and free cholesterol. Previously established ceramide ratios predicting cardiovascular mortality, or inflammation related eicosanoid lipids, were not altered. RG7652 treatment also affected the overall and relative distribution of lipids in lipoprotein classes. An overall decrease of total lipid species was observed in LDL and VLDL + IDL particles, while HDL-associated phospholipids increased. Following the treatment, LDL displayed reduced lipid cargo, whereas relative lipid proportions of the VLDL + IDL particles were mostly unchanged, and there were relatively more lipids carried in the HDL particles. CONCLUSIONS: Administration of PCSK9 antibody significantly alters the lipid composition of plasma and lipoprotein particles. These changes further shed light on the link between anti-PCSK9 therapies and cardiovascular risk.

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PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29365823
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[34] *Hong SJ, Choi SY, Han SH et al.* **Safety and tolerability of atorvastatin calcium anhydrous in Korean patients with dyslipidemia: An interim analysis from the lamp study**. Atherosclerosis 2017; 263:e236.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29365909
ABSTRACT

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PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29366104
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PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29365947
ABSTRACT

[37] *Karlson BW, Jornten-Karlsson M, Xu Y et al.* **Rationale, design, and baseline characteristics of a randomised trial evaluating the effect of a smart phone based patient support tool on treatment duration in patients prescribed rosuvastatin in china (EHELP China)**. Atherosclerosis 2017; 263:e247-e248.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29365946
ABSTRACT

[38] *Katamadze N, Golovina A, Berstein L et al.* **Estimates of carotid artery intima-media thickness and prevalence of atherosclerotic plaque in asymptomatic Russian subjects: Comparison with the results of the ARIC study**. Atherosclerosis 2017; 263:e143-e144.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29365571
ABSTRACT

[39] *Kurdi A, De Meyer GRY, Martinet W*. **Everolimus attenuates atherosclerotic plaque progression, intraplaque neovascularization, myocardial infarction and sudden death in a mouse model of advanced atherosclerosis**. Atherosclerosis 2017; 263:e59.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29366159
ABSTRACT

[40] *Logunova N, Gurina N, Boytsov S*. **Achievement of LDL-C goals in patients at moderate to very high cardiovascular risk on lipid-lowering drug therapy (cepheus II)**. Atherosclerosis 2017; 263:e236-e237.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29365910
ABSTRACT

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PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29366103
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ABSTRACT

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PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29365602
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PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29365942
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PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29365594
ABSTRACT

[49] *Mymin D, Salen G, Triggs-Raine B et al.* **The natural history of phytosterolemia: Observations on its homeostasis**. Atherosclerosis 2017; 269:122-128.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29353227
ABSTRACT
BACKGROUND AND AIMS: Phytosterolemia is a rare genetic disease caused by mutation of the ABCG5/8 gene. Our aim was to elucidate the natural history and homeostasis of phytosterolemia. METHODS: We analyzed a Hutterite kindred consisting of 21 homozygotes with phytosterolemia assembled over a period of two decades, all of whom carried the ABCG8 S107X mutation and were treated with ezetimibe. RESULTS: Most of these subjects were asymptomatic and devoid of clinical stigmata, and this, since they were ascertained primarily by a process of cascade testing, suggests that, relative to its true prevalence, phytosterolemia is a condition of low morbidity. All subjects have responded well to treatment with ezetimibe. Initial (pre-treatment) and post-ezetimibe levels of cholesterol and sitosterol were measured and percentage changes on ezetimibe were calculated. We found initial levels to be inversely related to subjects' ages as were percentage responses to ezetimibe therapy. There was also a direct correlation between initial levels and percentage responses to ezetimibe. Hence on-treatment levels were very uniform. CONCLUSIONS: This evidence of a link with age leads us to propose that an age-related change in cholesterol and sterol homeostasis occurs at puberty in phytosterolemia and that the change is due to high sterol and/or stanol levels causing feedback inhibition of sterol regulatory element-binding protein (SREBP-2) processing. This would explain the well-documented phenomenon of depressed cholesterol synthesis in phytosterolemia. It is also well-known that LDL-receptor activity is increased, and this feasibly explains reduced LDL levels and consequent reduction of plasma cholesterol and sitosterol levels. Downregulated SREBP-2 processing would be expected to also lower proprotein convertase subtilisin/kexin type 9 (PCSK9) levels and this would explain high LDL-receptor activity. The above state could be termed disrupted homeostasis and the alternative, seen mostly in children and characterized by hypercholesterolemia and hypersterolemia, simple homeostasis.

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ABSTRACT

Literature update week 04 (2018)

[51] *Nikolic T, Zivkovic V, Jeremic N et al.* **Impact of atorvastatin and simvastatin on lipid and non-lipid biochemical risk factors in diet-induced hyperhomocisteinemia in wistar albino rats: A comparative study**. Atherosclerosis 2017; 263:e136.
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[52] *Nizomov A, Kenjaev S*. **Effect of high-dose atorvastatin on lipid spectrum and inflammation in acute myocardial infarction**. Atherosclerosis 2017; 263:e245-e246.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29365940
ABSTRACT

[53] *Pek SLT, Dissanayake S, Fong JCW et al.* **Spectrum of mutations in index patients with familial hypercholesterolemia in Singapore: Single center study**. Atherosclerosis 2017; 269:106-116.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29353225
ABSTRACT
BACKGROUND AND AIMS: Familial hypercholesterolemia (FH) is an autosomal dominant genetic disease characterized by the presence of high plasma low density lipoproteins cholesterol (LDL-c). Patients with FH, with mutation detected, are at increased risk of premature cardiovascular disease compared to those without mutations. The aim of the study was to assess the type of mutations in patients, clinically diagnosed with FH in Singapore. METHODS: Patients (probands) with untreated/highest on-treatment LDL-c>4.9mmol/l were recruited (June 2015 to April 2017). Anthropometric, biochemical indices, blood and family history were collected. DNA was extracted and Next Generation Sequencing (NGS) was performed in 26 lipid-related genes, including LDLR, APOB and PCSK9, and validated using Sanger. Multiplex-ligation probe analyses for LDLR were performed to identify large mutation derangements. Based on HGVS nomenclature, LDLR mutations were classified as "Null"(nonsense, frameshift, large rearrangements) and "Defective"(point mutations which are pathogenic). RESULTS: Ninety-six probands were recruited: mean age: (33.5+/-13.6) years. 52.1% (n=50) of patients had LDLR mutations, with 15 novel mutations, and 4.2% (n=4) had APOB mutations. Total cholesterol (TC) and LDL-c were significantly higher in those with LDLR mutations compared to APOB and no mutations [(8.53+/-1.52) vs. (6.93+/-0.47) vs. (7.80+/-1.32)] mmol/l, p=0.012 and [(6.74+/-0.35) vs. (5.29+/-0.76) vs. (5.98+/-1.23)] mmol/l, p=0.005, respectively. Patients with "null LDLR" mutations (n=13) had higher TC and LDL-c than "defective LDLR" mutations (n=35): [(9.21+/-1.60) vs. (8.33+/-1.41)]mmol/l, p=0.034 and [(7.43+/-1.47) vs. (6.53+/-1.21)]mmol/l, p=0.017, respectively. CONCLUSIONS: To our knowledge, this is the first report of mutation detection in patients with clinically suspected FH by NGS in Singapore. While percentage of mutations is similar to other countries, the spectrum locally differs.

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[59] *Reiner Z*. **PCSK9 inhibitors in clinical practice: Expectations and reality**. Atherosclerosis 2018.
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ABSTRACT

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ABSTRACT

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PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29365486
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PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29366231
ABSTRACT

[73] *Yasuda H, Fujiwara A, Komiya S, Haze T*. **Effects of rosuvastatin add-on treatment on hyperlipidemia in type 2 diabetic patients with chronic kidney disease receiving ethyl icosapentate**. Atherosclerosis 2017; 263:e241-e242.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29365927
ABSTRACT

[74] *Zandl M, Fanaee-Danesh E, Gali CC et al.* **Interactions of simvastatin and APOJ with amyloid processing in cerebrovascular endothelial cells**. Atherosclerosis 2017; 263:e85-e86.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29366247
ABSTRACT

[75] *Zhu B, Tang C*. **Atorvastatin upregulates expression of p16 and inhibits proliferation and migration of VSMCS via altered dna methylation**. Atherosclerosis 2017; 263:e132.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29365530
ABSTRACT

[76] *Li GM, Zhao J, Li B et al.* **The anti-inflammatory effects of statins on patients with rheumatoid arthritis: A systemic review and meta-analysis of 15 randomized controlled trials**. Autoimmunity reviews 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29353098
ABSTRACT
BACKGROUND: Over the past several years, numerous studies investigated the anti-inflammatory effects of statin on patients with RA. However, the findings of the individual studies were often inconsistent or conflicting. MATERIALS AND METHODS: The Pubmed, Web of Science, Embase, Cochrane Library and CNKI literature databases were searched in order to identify randomized controlled clinical trials where the association between the anti-inflammatory effect of statin and RA was investigated. Two researchers performed data extraction from eligible independently. Quality parameters and risk of bias in the included studies were assessed according to Cochrane's guidelines. The pooled Standardized Mean Difference (SMD) with a 95%CI was used to assess the anti-inflammatory effect of statin in

patients with RA. RESULTS: Fifteen randomized controlled clinical, classified as "high quality" and with a relatively low risk of selection bias, were included in the meta-analysis. Of these, eight reported that there was no difference in the level of serum total lipids between the atorvastatin-treated and the conventional treatment group. However, the pooled analysis showed that atorvastatin could increase the level of serum amount of high-density lipoprotein (HDL) in RA patients by approximately x+/-SD95% [HDL: SMD=0.807, 95%CI=(0.187, 1.426), p=.011]. Meanwhile atorvastatin could reduce the level of serum low-density lipoprotein (LDL), total cholesterol (TC), and triglyceride (TG) in RA patient by x+/-SD95% [LDL: SMD=-4.015, 95%CI=(-5.848, -2.183), p=.000; TC: SMD=-4.497, 95%CI=(-6.457, -2.537), p=.000; TG: SMD=-1.475, 95%CI=(-2.352, -0.599), p=.001]. Nine studies reported a change in C-Reactive Protein (CRP) after atorvastatin treatment, and the pooled analysis showed that atorvastatin decreased CRP in RA patients by x+/-SD95% [SMD=-3.033, 95%CI=(-4.460, -1.606), p=.000]. Seven studies investigated the change of Erythrocyte Sedimentation Rate (ESR), and the pooled analysis showed that atorvastatin decreased ESR by x+/-SD95% [SMD=-2.097, 95%CI=(-3.408, -0.786), p=.002]. Nine studies reported the improvement of disease activity score in RA patients after taking atorvastatin for 12weeks, and the pooled analysis showed atorvastatin could decrease the DAS28 score in RA patients by x+/-SD95% [SMD=-2.001, 95%CI=(-3.191, -0.811), p=.001]. CONCLUSIONS: Statins have a significant anti-inflammatory effect in RA patients. However, atorvastatin was superior to simvastatin both in terms of its anti-inflammatory and lipid-lowering activities.

[77] *Shahim B, Gyberg V, De Bacquer D et al.* **Undetected dysglycaemia common in primary care patients treated for hypertension and/or dyslipidaemia: on the need for a screening strategy in clinical practice. A report from EUROASPIRE IV a registry from the EuroObservational Research Programme of the European Society of Cardiology**. Cardiovascular diabetology 2018; 17:21.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29368616
ABSTRACT
BACKGROUND: Dysglycaemia defined as type 2 diabetes (T2DM) and impaired glucose tolerance (IGT), increases the risk of cardiovascular disease (CVD). The negative impact is more apparent in the presence of hypertension and/or dyslipidaemia. Thus, it seems reasonable to screen for dysglycaemia in patients treated for hypertension and/or dyslipidaemia. A simple screening algorithm would enhance the adoption of such strategy in clinical practice. OBJECTIVES: To test the hypotheses (1) that dysglycaemia is common in patients with hypertension and/or dyslipidaemia and (2) that initial screening with the Finnish Diabetes Risk Score (FINDRISC) will decrease the need for laboratory based tests. METHODS: 2395 patients (age 18-80 years) without (i) a history of CVD or TDM2, (ii) prescribed blood pressure and/or lipid lowering drugs answered the FINDRISC questionnaire and had an oral glucose tolerance test (OGTT) and HbA1c measured. RESULTS: According to the OGTT 934 (39%) had previously undetected dysglycaemia (T2DM 19%, IGT 20%). Of patients, who according to FINDRISC had a low, moderate or slightly elevated risk 20, 34 and 41% and of those in the high and very high-risk category 49 and 71% had IGT or T2DM respectively. The OGTT identified 92% of patients with T2DM, FPG + HbA1c 90%, FPG 80%, 2hPG 29% and HbA1c 22%. CONCLUSIONS: (1) The prevalence of dysglycaemia was high in patients treated for hypertension and/or dyslipidaemia.

(2) Due to the high proportion of dysglycaemia in patients with low to moderate FINDRISC risk scores its initial use did not decrease the need for subsequent glucose tests. (3) FPG was the best test for detecting T2DM. Its isolated use is limited by the inability to disclose IGT. A pragmatic strategy, decreasing the demand for an OGTT, would be to screen all patients with FPG followed by OGTT in patients with IFG.

[78] *Ouyang XJ, Zhang YQ, Chen JH et al.* **Situational Analysis of Low-density Lipoprotein Cholesterol Control and the Use of Statin Therapy in Diabetes Patients Treated in Community Hospitals in Nanjing, China**. Chinese medical journal 2018; 131:295-300.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29363644
ABSTRACT
BACKGROUND: Comprehensive management of diabetes should include management of its comorbid conditions, especially cardiovascular complications, which are the leading cause of morbidity and mortality among patients with diabetes. Dyslipidemia is a comorbid condition of diabetes and a risk factor for cardiovascular complications. Therefore, lipid level management is a key of managing patients with diabetes successfully. However, it is not clear that how well dyslipidemia is managed in patients with diabetes in local Chinese health-care communities. This study aimed to assess how well low-density lipoprotein cholesterol (LDL-C) was managed in Nanjing community hospitals, China. METHODS: We reviewed clinical records of 7364 diabetic patients who were treated in eleven community hospitals in Nanjing from October 2005 to October 2014. Information regarding LDL-C level, cardiovascular risk factors, and use of lipid-lowering agents were collected. RESULTS: In patients without history of cardiovascular disease (CVD), 92.1% had one or more CVD risk factors, and the most common CVD risk factor was dyslipidemia. The overall average LDL-C level was 2.80 +/- 0.88 mmol/L, which was 2.62 +/- 0.90 mmol/L and 2.82 +/- 0.87 mmol/L in patients with and without CVD history respectively. Only 38% of all patients met the target goal and 37.3% of patients who took lipid-lowering agents met target goal. Overall, 24.5% of all patients were on lipid-lowering medication, and 36.3% of patients with a CVD history and 20.9% of patients without CVD history took statins for LDL-C management. The mean statin dosage was 13.9 +/- 8.9 mg. CONCLUSIONS: Only a small portion of patients achieved target LDL-C level, and the rate of using statins to control LDL-C was low. Managing LDL-C with statins in patients with diabetes should be promoted, especially in patients without a CVD history and with one or more CVD risk factors.

[79] *Simes J, Robledo KP, White HD et al.* **D-dimer Predicts Long-Term Cause-Specific Mortality, Cardiovascular Events and Cancer in Stable Coronary Heart Disease Patients: The LIPID Study**. Circulation 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29367425
ABSTRACT
Background -D-dimer, a degradation product of cross-linked fibrin, is a marker for hypercoagulability and thrombotic events. Moderately elevated levels of D-dimer are associated with the risk of venous and arterial events in patients with vascular disease. We assessed the role of D-dimer levels in predicting long-term vascular outcomes, cause-specific mortality, and new cancers in the LIPID trial in the context of other risk factors. Methods -LIPID randomized patients to placebo or pravastatin 40 mg/day 5-38 months after myocardial

infarction or unstable angina. D-dimer levels were measured at baseline and at 1 year. Median follow-up was 6.0 years during the trial and 16 years in total. Results -Baseline D-dimer levels for 7863 patients were grouped by quartile (</=112, 112-173, 173-273, >273 ng/mL). Higher levels were associated with older age, female sex, history of hypertension, poor renal function and elevated levels of B-natriuretic peptide, high-sensitivity C-reactive protein, and sensitive troponin I (each P<0.001). During the first 6 years, after adjustment for up to 30 additional risk factors, higher D-dimer was associated with a significantly increased risk of a major coronary event (Q4 vs Q1 HR 1.45; 95% CI 1.21-1.74), major cardiovascular (CVD) event (HR 1.45; 95% CI 1.23-1.71) and venous thromboembolism (HR 4.03 (2.31-7.03; 95% CI 2.31-7.03); each P<0.001. During the 16 years overall, higher D-dimer was an independent predictor of all-cause mortality (HR 1.59), CVD mortality (1.61), cancer mortality (1.54) and non-CVD noncancer mortality (1.57) (each P<0.001), remaining significant for deaths from each cause occurring beyond 10 years of follow-up (each P</=0.01). Higher D-dimer also independently predicted an increase in cancer incidence (HR 1.16, P=0.02).The D-dimer level increased the net reclassification index for all-cause mortality by 4.0 and venous thromboembolism by 13.6. Conclusions -D-dimer levels predict long-term risk of arterial and venous events, CVD mortality, and non-CVD noncancer mortality, independently of other risk factors. D-dimer is also a significant predictor of cancer incidence and mortality. These results support an association of D-dimer with fatal events across multiple diseases and demonstrate that this link extends beyond 10 years' follow-up.

[80] *Budoff M, Brent Muhlestein J, Le VT et al.* **Effect of Vascepa (icosapent ethyl) on progression of coronary atherosclerosis in patients with elevated triglycerides (200-499 mg/dL) on statin therapy: Rationale and design of the EVAPORATE study**. Clinical cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29365351
ABSTRACT
Despite reducing progression and promoting regression of coronary atherosclerosis, statin therapy does not fully address residual cardiovascular (CV) risk. High-purity eicosapentaenoic acid (EPA) added to a statin has been shown to reduce CV events and induce regression of coronary atherosclerosis in imaging studies; however, data are from Japanese populations without high triglyceride (TG) levels and baseline EPA serum levels greater than those in North American populations. Icosapent ethyl is a high-purity prescription EPA ethyl ester approved at 4 g/d as an adjunct to diet to reduce TG levels in adults with TG levels >499 mg/dL. The objective of the randomized, double-blind, placebo-controlled EVAPORATE study is to evaluate the effects of icosapent ethyl 4 g/d on atherosclerotic plaque in a North American population of statin-treated patients with coronary atherosclerosis, TG levels of 200 to 499 mg/dL, and low-density lipoprotein cholesterol levels of 40 to 115 mg/dL. The primary endpoint is change in low-attenuation plaque volume measured by multidetector computed tomography angiography. Secondary endpoints include incident plaque rates; quantitative changes in different plaque types and morphology; changes in markers of inflammation, lipids, and lipoproteins; and the relationship between these changes and plaque burden and/or plaque vulnerability. Approximately 80 patients will be followed for 9 to 18 months. The clinical implications of icosapent ethyl 4 g/d treatment added to statin therapy on CV endpoints are being evaluated in the large CV outcomes study REDUCE-IT. EVAPORATE will provide important

imaging-derived data that may add relevance to the clinically derived outcomes from REDUCE-IT.

[81] *Helou TN, Santos RD, Laurinavicius AG et al.* **Association between clinical factors and self-underestimation of cardiovascular risk in subjects submitted to a routine health evaluation**. Clinical cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29356017
ABSTRACT
BACKGROUND: The perception of cardiovascular (CV) risk is essential for adoption of healthy behaviors. However, subjects underestimate their own risk. HYPOTHESIS: Clinical characteristics might be associated with self-underestimation of CV risk. METHODS: This is a retrospective, cross-sectional study of individuals submitted to routine health evaluation between 2006 and 2012, with calculated lifetime risk score (LRS) indicating intermediate or high risk for CV disease (CVD). Self-perception of risk was compared with LRS. Logistic regression analysis was performed to test the association between clinical characteristics and subjective underestimation of CV risk. RESULTS: Data from 5863 subjects (age 49.4 +/- 7.1 years; 19.9% female) were collected for analysis. The LRS indicated an intermediate risk for CVD in 45.7% and a high risk in 54.3% of individuals. The self-perception of CV risk was underestimated compared with the LRS in 4918 (83.9%) subjects. In the adjusted logistic regression model, age (odds ratio [OR]: 1.28, 95% confidence interval [CI]: 1.10-1.47 per 10 years, P = 0.001), smoking (OR: 1.99, 95% CI: 1.40-2.83, P < 0.001), dyslipidemia (OR: 1.21, 95% CI: 1.01-1.46, P = 0.045), physical activity (OR: 1.66, 95% CI: 1.36-2.02, P < 0.001), and use of antihypertensive (OR: 1.49, 95% CI: 1.15-1.92, P = 0.002) and lipid-lowering medications (OR: 2.13, 95% CI: 1.56-2.91, P < 0.001) were associated with higher chance of risk underestimation, whereas higher body mass index (OR: 0.92, 95% CI: 0.90-0.94, P < 0.001), depressive symptoms (OR: 0.46, 95% CI: 0.37-0.57, P < 0.001), and stress (OR: 0.41, 95% CI: 0.33-0.50, P < 0.001) decreased the chance. CONCLUSIONS: Among individuals submitted to routine medical evaluation, aging, smoking, dyslipidemia, physical activity, and use of antihypertensive and lipid-lowering medications were associated with higher chance of CV risk underestimation. Subjects with these characteristics may benefit from a more careful risk orientation.

[82] *Thomas IC, Forbang NI, Criqui MH*. **The evolving view of coronary artery calcium and cardiovascular disease risk**. Clinical cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29356018
ABSTRACT
Calcification of the coronary artery is a complex pathophysiologic process that is intimately associated with atherosclerosis. Extensive investigation has demonstrated the value of identifying and quantifying coronary artery calcium (CAC) in atherosclerotic cardiovascular disease (CVD) prognostication. However, over the last several years, an increasing body of evidence has suggested that CAC has underappreciated aspects that modulate, and at times attenuate, future CVD risk. The most commonly used measure of CAC, the Agatston unit, effectively models both higher density and higher area of CAC as risk factors for future CVD events. Recent findings from the Multi-Ethnic Study of Atherosclerosis (MESA) have challenged this assumption, demonstrating that higher density of CAC is protective for coronary heart

disease and CVD events. Statins may be associated with an increase in CAC, an unexpected finding given their clear benefits in the prevention and treatment of CVD. Studies utilizing intracoronary ultrasound and coronary computed tomography angiography have demonstrated that calcified atherosclerotic plaque-as compared with noncalcified or sparsely calcified plaque-is associated with fewer CVD events. These studies lend support to the often-asserted (but as yet unvalidated) view that calcification may play a role in plaque stabilization. Furthermore, vascular calcification, though a surrogate for atherosclerotic plaque burden, may also possess identifiable aspects that can refine CVD risk assessment.

[83] *Ward NC, Pang J, Ryan JDM, Watts GF*. **Nutraceuticals in the management of patients with statin-associated muscle symptoms, with a note on real-world experience**. Clinical cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29363784
ABSTRACT
There is considerable evidence for the role of low-density lipoprotein cholesterol (LDL-C) in the development of atherosclerotic cardiovascular disease. Although statin therapy remains the most frequency prescribed medication to reduce LDL-C and lower risk of cardiovascular disease, a considerable number of patients develop muscle-related side affects. This review summarizes recent literature supporting the role of nutraceuticals as LDL-C-lowering therapy in statin-intolerant patients, with evidence from our own clinical practices.

[84] *Kasichayanula S, Grover A, Emery MG et al.* **Clinical Pharmacokinetics and Pharmacodynamics of Evolocumab, a PCSK9 Inhibitor**. Clinical pharmacokinetics 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29353350
ABSTRACT
Proprotein convertase subtilisin/kexin type 9 (PCSK9) increases plasma low-density lipoprotein cholesterol (LDL-C) by decreasing expression of the LDL receptor on hepatic cells. Evolocumab is a human monoclonal immunoglobulin G2 that binds specifically to human PCSK9 to reduce LDL-C. Evolocumab exhibits nonlinear kinetics as a result of binding to PCSK9. Elimination is predominantly through saturable binding to PCSK9 at lower concentrations and a nonsaturable proteolytic pathway at higher concentrations. The effective half-life of evolocumab is 11-17 days. The pharmacodynamic effects of evolocumab on PCSK9 are rapid, with maximum suppression within 4 h. At steady state, peak reduction of LDL-C occurs approximately 1 week after a subcutaneous dose of 140 mg every 2 weeks (Q2W) and 2 weeks after a subcutaneous dose 420 mg once monthly (QM), and returns towards baseline over the dosing interval. In several clinical studies, these doses of evolocumab reduced LDL-C by approximately 55-75% compared with placebo. Evolocumab also reduced lipoprotein(a) [Lp(a)] levels and improved those of other lipids in clinical studies. No clinically meaningful differences in pharmacodynamic effects on LDL-C were observed in adult subjects regardless of mild/moderate hepatic impairment, renal impairment or renal failure, body weight, race, sex, or age. No clinically meaningful differences were observed for the pharmacodynamic effects of evolocumab on LDL-C between patients who received evolocumab alone or in combination with a statin, resulting in additional lowering of LDL-C when evolocumab was combined with a statin. No dose adjustment is necessary based on patient-specific factors or concomitant medication use.

[85] *Volta A, Hovingh GK, Grefhorst A*. **Genetics of familial hypercholesterolemia: a tool for development of novel lipid lowering pharmaceuticals?** Current opinion in lipidology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29356705
ABSTRACT
PURPOSE OF REVIEW: Familial hypercholesterolemia is characterized by high LDL cholesterol and an elevated risk to develop coronary heart disease. Mutations in LDL receptor-mediated cholesterol uptake are the main cause of familial hypercholesterolemia. However, multiple mutations in various other genes are also associated with high LDL cholesterol and even familial hypercholesterolemia. Thus, pharmaceuticals that target these genes and proteins might be attractive treatment options to reduce LDL cholesterol. This review provides an overview of the recent developments and clinical testing of such pharmaceuticals. RECENT FINDINGS: About 80 genes are associated with hypercholesterolemia but only pharmaceuticals that inhibit cholesteryl ester transfer protein (CETP), angiopoietin-related protein 3 (ANGPTL3), and apolipoprotein C-III (apoC-III) have recently been tested in clinical trials. Inhibition of CETP and ANGPTL3 lowered LDL cholesterol. ANGPTL3 inhibition had the largest effect and was even effective in familial hypercholesterolemia patients. The effect of apoC-III inhibition on LDL cholesterol is not conclusive. SUMMARY: Of the many potential pharmaceutical targets involved in LDL cholesterol, only a few have been studied so far. Of these, pharmaceuticals that inhibit CETP or ANGPTL3 are promising novel treatment options to reduce LDL cholesterol but the effect of apoC-III inhibition requires more research.

[86] *Steinberg GR*. **Cellular Energy Sensing and Metabolism-Implications for Treating Diabetes: The 2017 Outstanding Scientific Achievement Award Lecture**. Diabetes 2018; 67:169-179.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29358486
ABSTRACT
The Outstanding Scientific Achievement Award recognizes distinguished scientific achievement in the field of diabetes, taking into consideration independence of thought and originality. Gregory R. Steinberg, PhD, professor of medicine, Canada Research Chair, J. Bruce Duncan Endowed Chair in Metabolic Diseases, and codirector of the Metabolism and Childhood Obesity Research Program at McMaster University, Hamilton, Ontario, Canada, received the prestigious award at the American Diabetes Association's 77th Scientific Sessions, 9-13 June 2017, in San Diego, CA. He presented the Outstanding Scientific Achievement Award Lecture, "Cellular Energy Sensing and Metabolism-Implications for Treating Diabetes," on Monday, 12 June 2017.The survival of all cells is dependent on the constant challenge to match energetic demands with nutrient availability, a task that is mediated through a highly conserved network of metabolic fuel sensors that orchestrate both cellular and whole-organism energy balance. A mismatch between cellular energy demand and nutrient availability is a key factor contributing to the development of type 2 diabetes; thus, understanding the fundamental mechanisms by which cells sense nutrient availability and demand may lead to the development of new treatments. Glucose-lowering therapies, such as caloric restriction, exercise, and metformin, all induce an energetic challenge that results in the activation of the cellular energy sensor AMP-activated protein kinase (AMPK). Activation of AMPK in turn suppresses lipid synthesis and inflammation while increasing glucose uptake, fatty acid oxidation, and mitochondrial function.

In contrast, high levels of nutrient availability suppress AMPK activity while also increasing the production of peripheral serotonin, a gut-derived endocrine factor that suppresses beta-adrenergic-induced activation of brown adipose tissue. Identifying new ways to manipulate these two ancient fuel gauges by activating AMPK and inhibiting peripheral serotonin may lead to the development of new therapies for treating type 2 diabetes.

[87] *Cheng Y, Zheng H, Wang B et al.* **Sorafenib and fluvastatin synergistically alleviate hepatic fibrosis via inhibiting the TGFbeta1/Smad3 pathway**. Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver 2017.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29373239
ABSTRACT
BACKGROUND: Effective strategies for the treatment of hepatic fibrosis are urgently in need. AIMS: To investigate the effect of the co-treatment of sorafenib and fluvastatin on hepatic fibrosis and the underlying mechanisms. METHODS: A diethylnitrosamine-induced hepatic fibrosis rat model was used to evaluate the anti-fibrosis effect. Epithelial mesenchymal transition (EMT) of hepatocytes and hepatic stellate cells (HSCs) in response to sorafenib and fluvastatin was explored. A co-treatment effect on TGFbeta1 expression was explored in the Kupffer cells of rats. The effect of co-treatment on the regulation of the TGFbeta1/Smad3 pathway was investigated in both L02 cells and LX-2 cells. RESULTS: Sorafenib and fluvastatin synergistically reduced collagen content, alpha-SMA expression, lamin level, and hyaluronic acid level in the rat hepatic model. Combination treatment significantly inhibited the expression of mesenchymal markers and promoted the expression of epithelial markers in hepatocytes. Co-treatment statistically suppressed the production of TGFbeta1 in Kupffer cells. Suppression of EMT in parallel with alleviated up-regulation of fibronectin and alpha-SMA expression was observed in TGFbeta1-activated LX-2 cells. Mechanistically, sorafenib plus fluvastatin blocked the TGFbeta1/Smad3 signaling pathway via inhibiting phosphorylation of TbetaR II in hepatocytes and HSCs. CONCLUSIONS: Sorafenib and fluvastatin synergistically alleviated diethylnitrosamine-induced hepatic fibrosis in rats. Sorafenib plus fluvastatin may be a potential combination treatment for hepatic fibrotic diseases.

[88] *Ghaleb Y, Elbitar S, El Khoury P et al.* **Usefulness of the genetic risk score to identify phenocopies in families with familial hypercholesterolemia?** Eur J Hum Genet 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29374275
ABSTRACT
Familial hypercholesterolemia (FH) is caused by mutations in LDLR (low-density lipoprotein receptor), APOB (apolipoprotein B), PCSK9 (proprotein convertase subtilisin/kexin type 9), or APOE (apolipoprotein E) genes in approximately 80% of the cases. Polygenic forms of hypercholesterolemia may be present among patients clinically diagnosed with FH but with no identified mutation (FH mutation-negative (FH/M-)). To address whether polygenic forms may explain phenocopies in FH families, we calculated a 6-single-nucleotide polymorphism (SNP) genetic risk score (GRS) in all members from five French FH families where a mutation was identified (FH/M+) as well as some phenocopies (FH/M-). In two families, three FH/M- patients present a high GRS suggesting a polygenic hypercholesterolemia for these phenocopies.

However, a high GRS is also observed in nine FH/M+ patients and in four unaffected relatives from three families. These observations indicate that the GRS does not seem to be a good diagnostic tool at the individual level. Nevertheless, the GRS seems to be a contributor of the severity of hypercholesterolemia since patients who cumulate a mutation and a high GRS exhibit higher low-density lipoprotein cholesterol levels when compared to patients with only FH (p = 0.054) or only polygenic hypercholesterolemia (p = 0.0039). In conclusion, the GRS can be used as a marker of the severity of hypercholesterolemia but does not seem to be a reliable tool to distinguish phenocopies within FH families.

[89] *Tamura S, Koike Y, Takeda H et al.* **Ameliorating effects of D-47, a newly developed compound, on lipid metabolism in an animal model of familial hypercholesterolemia (WHHLMI rabbits)**. European journal of pharmacology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29355561
ABSTRACT
Improvements induced in lipid metabolism in the liver by D-47, a newly developed compound, were examined herein. WHHLMI rabbits, an animal model of hypercholesterolemia and coronary atherosclerosis, was fed D-47-supplemented chow for 5 weeks at a dose of 30mg/kg. Lipid concentration were assayed using enzymatic methods. Plasma lipoproteins were fractionated with an ultracentrifuge. mRNA expression was analyzed with real-time PCR. Lipidome analyses of lipoproteins were performed using supercritical fluid chromatography mass spectrometry. In the D-47-treated group, serum lipid levels decreased by 23% for total cholesterol and by 40% for triglycerides. These reductions were mainly attributed to decreases in the VLDL fraction. Compared with the control, in the D-47 group, lipid contents in the liver were decreased by 22% in cholesterol and by 69% in triglycerides, and fat accumulation was decreased by 57% in pericardial fat and by 17% in mesenteric fat. In lipidome analyses of VLDL fraction, lysophosphatidylcholine, phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol, phosphatidylethanolamine plasmalogen, sphingomyelin, and ceramide were decreased by the D-47 treatment. mRNA expression in the liver was 51% lower for FAS and 24% lower for MTP, but 5.9- and 5.1-fold higher for CYP7A1 and CPT-1, respectively, in the D-47 group than in the control. mRNA expression was 72%, 64%, and 36% higher for LPL, CTP-1, and PPARgamma, respectively, in mesenteric fat in the D-47 group. D-47 is a potent lipid-lowering compound that uses a different mechanism of action from that of statins. It has potential as a compound in the treatment of steatohepatitis and metabolic syndrome.

[90] *Bao JW, Sun B, Ma PP et al.* **Rosuvastatin inhibits inflammatory response and resists fibrosis after myocardial infarction**. European review for medical and pharmacological sciences 2018; 22:238-245.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29364492
ABSTRACT
OBJECTIVE: To study the effect of rosuvastatin on myocardial infarction in rats and its mechanism of action. MATERIALS AND METHODS: 24 Sprague-Dawley (SD) rats were randomly divided into 3 groups: intensive statin group (n=8), myocardial infarction control group (n=8) and sham-operation group (n=8). The left anterior descending coronary artery was ligated to establish myocardial infarction models. Rats in intensive statin group were treated with gavage

via rosuvastatin (1 mg x kg) and 1.5 mL distilled water suspension at 3 d before operation, while rats in the other two groups received gavage via the same amount of distilled water till 4 weeks after operation. Venous blood was collected using capillary glass tubes at 3 d before operation (before medication) and the last day in the 4th week after operation. Interleukin-6 (IL-6) was detected via chemiluminescence assay, and tumor necrosis factor-alpha (TNF-alpha) was detected via immunofluorescence assay. Hematoxylin and eosin (HE) staining and Masson staining were performed for myocardium to detect the inflammation and fibrosis. Finally, the expressions of inflammatory protein p65, peroxisome proliferator-activated receptor (PPAR) and fibrin were detected via Western blotting, and the Snail expression was detected by immunohistochemical assay. RESULTS: The survival rate and cardiac function of rats in intensive statin group were superior to those in control group. HE staining and detection of blood IL-6 and TNF-alpha, and p65 and PPAR protein expressions revealed that the inflammatory levels in the body and myocardium of rats in intensive statin group were decreased compared with those in control group. Masson staining and detection of fibrin level showed that the myocardial fibrosis level of rats in intensive statin group was reduced compared with that in control group. CONCLUSIONS: Rosuvastatin can reduce the level of myocardial fibrosis through alleviating the inflammatory response in rats with myocardial infarction.

[91] *Santhakumar AB, Battino M, Alvarez-Suarez JM*. **Dietary polyphenols: Structures, bioavailability and protective effects against atherosclerosis**. Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29360556
ABSTRACT
Epidemiological studies have demonstrated that nutritional habits, like those based on high consumption of fruits and vegetables, have been associated with a longer life expectancy and a significant decrease in the incidence and prevalence of several chronic diseases with inflammatory basis, such as cardiovascular diseases (CVD). This beneficial activity has been related to the content of several bioactive compounds in fruit and vegetables, such as polyphenols. The cardioprotective effects of polyphenols have been linked mainly to its antioxidant properties; however, recent findings attribute its anti-atherosclerotic potential to modulate simultaneous signaling and mechanistic pathways. Emerging data suggest that polyphenols can regulate cellular lipid metabolism; vascular and endothelial function; haemostasis; as well as platelet function; which represent primary conditions for atherosclerotic plaque formation and development. This review presents the results of a selection of experimental studies and clinical trials regarding the atheroprotective effects of the most common dietary polyphenols.

[92] *Ni Chroinin D, Ni Chroinin C, Akijian L et al.* **Suboptimal lipid management before and after ischaemic stroke and TIA-the North Dublin Population Stroke Study**. Irish journal of medical science 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29368282
ABSTRACT

BACKGROUND: Few population-based studies have assessed lipid adherence to international guidelines for primary and secondary prevention in stroke/transient ischaemic attack (TIA) patients. AIMS: This study aims to evaluate adherence to lipid-lowering therapy (LLT) guidelines amongst patients with ischaemic stroke/TIA. METHODS: Using hot and cold pursuit methods from multiple hospital/community sources, all stroke and TIA cases in North Dublin City were prospectively ascertained over a 1-year period. Adherence to National Cholesterol Education Programme (NCEP) III guidelines, before and after index ischaemic stroke/TIA, was assessed. RESULTS: Amongst 616 patients (428 ischaemic stroke, 188 TIA), total cholesterol was measured following the qualifying event in 76.5% (471/616) and low-density lipoprotein (LDL) in 60.1% (370/616). At initial stroke/TIA presentation, 54.1% (200/370) met NCEP III LDL goals. Compliance was associated with prior stroke (odds ratio [OR] 2.19, p = 0.02), diabetes (OR 1.91, p = 0.04), hypertension (OR 1.57, p = 0.03), atrial fibrillation (OR 1.78, p = 0.01), pre-event LLT (OR 2.85, p < 0.001) and higher individual LDL goal (p = 0.001). At stroke/TIA onset, 32.7% (195/596) was on LLT. Nonetheless, LDL exceeded individual NCEP goal in 29.2% (56/192); 21.6% (53/245) warranting LLT was not on treatment prior to stroke/TIA onset. After index stroke/TIA, 75.9% (422/556) was on LLT; 15.3% (30/196) meeting NCEP III criteria was not prescribed a statin as recommended. By 2 years, actuarial survival was 72.8% and 11.9% (59/497) experienced stroke recurrence. No association was observed between initial post-event target adherence and 2-year outcomes. CONCLUSIONS: In this population-based study, LLT recommended by international guidelines was under-used, before and after index stroke/TIA. Strategies to improve adherence are needed.

[93] *Ong KL, Waters DD, Fayyad R et al.* **Relationship of High-Density Lipoprotein Cholesterol With Renal Function in Patients Treated With Atorvastatin**. Journal of the American Heart Association 2018; 7.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29358194
ABSTRACT
BACKGROUND: It is not known whether the concentration of high-density lipoprotein (HDL) cholesterol is related to renal function in statin-treated patients. We therefore investigated whether HDL cholesterol levels predicted renal function in atorvastatin-treated patients in the TNT (Treating to New Targets) trial. METHODS AND RESULTS: A total of 9542 participants were included in this analysis. Renal function was assessed by estimated glomerular filtration rate (eGFR). HDL cholesterol levels at month 3 were used as this is the time point at which on-treatment HDL cholesterol levels became stable. Among 6319 participants with a normal eGFR (>/=60 mL/min per 1.73 m(2)) at baseline, higher HDL cholesterol levels at month 3 were significantly associated with lower risk of decline in eGFR (ie, having eGFR <60 mL/min per 1.73 m(2)) during follow-up (HR of 1.04, 0.88, 0.85, and 0.77 for HDL cholesterol quintiles 2, 3, 4, and 5, respectively, relative to quintile 1, P for trend=0.006). Among 3223 participants with an eGFR (<60 mL/min per 1.73 m(2)) at baseline, higher HDL cholesterol levels at month 3 had less impact on eGFR during follow-up, with statistical significance observed only when analyzing HDL cholesterol levels as a continuous variable (P=0.043), but not as a categorical quintile variable (P for trend=0.27). CONCLUSIONS: In patients treated with atorvastatin, higher HDL cholesterol levels were associated with lower risk of eGFR decline in patients with normal eGFR at baseline. However, further study is needed to establish whether there is any causal

relationship between HDLs and renal function. CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT00327691.

[94] *Salami JA, Warraich HJ, Valero-Elizondo J et al.* **National Trends in Nonstatin Use and Expenditures Among the US Adult Population From 2002 to 2013: Insights From Medical Expenditure Panel Survey**. Journal of the American Heart Association 2018; 7.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29358195
ABSTRACT
BACKGROUND: Evidence supporting nonstatin lipid-lowering therapy in atherosclerotic cardiovascular disease risk reduction is variable. We aim to examine nonstatin utilization and expenditures in the United States between 2002 and 2013. METHODS AND RESULTS: We used the Medical Expenditure Panel Survey database to estimate national trends in nonstatin use and cost (total and out-of-pocket, adjusted to 2013 US dollars using a gross domestic product deflator) among adults 40 years or older. Nonstatin users increased from 3 million (2.5%) in 2002-2003 (20.1 million prescriptions) to 8 million (5.6%) in 2012-2013 (45.8 million prescriptions). Among adults with atherosclerotic cardiovascular disease, nonstatin use increased from 7.5% in 2002-2003 to 13.9% in 2012-2013 after peaking at 20.3% in 2006-2007. In 2012-2013, 15.9% of high-intensity statin users also used nonstatins, versus 9.7% of low/moderate-intensity users and 3.6% of statin nonusers. Nonstatin use was significantly lower among women (odds ratio 0.80; 95% confidence interval 0.75-0.86), racial/ethnic minorities (odds ratio 0.41; 95% confidence interval 0.36-0.47), and the uninsured (odds ratio 0.47; 95% confidence interval 0.40-0.56). Total nonstatin expenditures increased from $1.7 billion (out-of-pocket cost, $0.7 billion) in 2002-2003 to $7.9 billion (out-of-pocket cost $1.6 billion) in 2012-2013, as per-user nonstatin expenditure increased from $550 to $992. Nonstatin expenditure as a proportion of all lipid-lowering therapy expenditure increased 4-fold from 8% to 32%. CONCLUSIONS: Between 2002 and 2013, nonstatin use increased by 124%, resulting in a 364% increase in nonstatin-associated expenditures.

[95] *Nomura A, Tada H, Nohara A et al.* **Oral Fat Tolerance Test for Sitosterolemia and Familial Hypercholesterolemia: A Study Protocol**. Journal of atherosclerosis and thrombosis 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29353827
ABSTRACT
AIM: Sitosterolemia is an extremely rare, autosomal recessive disease characterized by high plasma cholesterols and plant sterols because of increased absorption of dietary cholesterols and sterols from the intestine, and decreased excretion from biliary tract. Previous study indicated that sitosterolemic patients might be vulnerable to post-prandial hyperlipidemia, including high remnant-like lipoprotein particles (RLP) level. Here we evaluate whether a loading dietary fat increases a post-prandial RLP cholesterol level in sitosterolemic patients compared to heterozygous familial hypercholesterolemic patients (FH). METHODS: We recruit total of 20 patients: 5 patients with homozygous sitosterolemia, 5 patients with heterozygous sitosterolemia, and 10 patients with heterozygous FH as controls from May 2015 to March 2018 at Kanazawa University Hospital, Japan. All patients receive Oral Fat Tolerance Test (OFTT) cream (50 g/body surface area square meter, orally only once, and the cream includes 34% of fat, 74 mg of cholesterol, and rich in palmitic and oleic acids. The primary endpoint is the

change of a RLP cholesterol level after OFTT cream loading between sitosterolemia and FH. We measure them at baseline, and 2, 4, and 6 hours after the oral fat loading. RESULTS: This is the first study to evaluate whether sitosterolemia patients have a higher post-prandial RLP cholesterol level compared to heterozygous FH patients. CONCLUSION: The result may become an additional evidence to restrict dietary cholesterols for sitosterolemia. This study is registered at University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN ID: UMIN000020330).

[96] *Yao Y, Li B, Yin C et al.* **A Folate-Conjugated Dual-Modal Fluorescent Magnetic Resonance Imaging Contrast Agent that Targets Activated Macrophages In Vitro and In Vivo**. Journal of biomedical nanotechnology 2016; 12:2161-2171.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29372808
ABSTRACT
Mucin-1 (MUC1), a transmembrane glycoprotein is aberrantly expressed on approximately 90% of breast cancer and is an excellent target for nanoparticulate targeted imaging. In this study, the development of a dye-doped NIR emitting mesoporous silica nanoparticles platform conjugated to tumor-specific MUC1 antibody (ab-tMUC1-NIR-MSN) for in vivo optical detection of breast adenocarcinoma tissue is reported. The structural properties, the in vitro and in vivo performance of this nanoparticle-based probe were evaluated. In vitro studies showed that the MSN-based optical imaging nanoprobe is non-cytotoxic and targets efficiently mammary cancer cells overexpressing human tMUC1 protein. In vivo experiments with female C57BL/6 mice indicated that this platform accumulates mainly in the liver and did not induce short-term toxicity. In addition, we demonstrated that the ab-tMUC1-NIR-MSN nanoprobe specifically detects mammary gland tumors overexpressing human tMUC1 in a human MUC1 transgenic mouse model.

[97] *Chistiakov DA, Grechko AV, Myasoedova VA et al.* **The role of monocytosis and neutrophilia in atherosclerosis**. Journal of cellular and molecular medicine 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29364567
ABSTRACT
Monocytosis and neutrophilia are frequent events in atherosclerosis. These phenomena arise from the increased proliferation of hematopoietic stem and multipotential progenitor cells (HSPCs) and HSPC mobilization from the bone marrow to other immune organs and circulation. High cholesterol and inflammatory signals promote HSPC proliferation and preferential differentiation to the myeloid precursors (i.e., myelopoiesis) that than give rise to pro-inflammatory immune cells. These cells accumulate in the plaques thereby enhancing vascular inflammation and contributing to further lesion progression. Studies in animal models of atherosclerosis showed that manipulation with HSPC proliferation and differentiation through the activation of LXR-dependent mechanisms and restoration of cholesterol efflux may have a significant therapeutic potential.

[98] *Kaysen GA, Grimes B, Dalrymple LS et al.* **Associations of lipoproteins with cardiovascular and infection-related outcomes in patients receiving hemodialysis**. Journal of clinical lipidology 2017.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29361496

ABSTRACT

BACKGROUND: In hemodialysis (HD) patients, higher lipid levels are associated with lower mortality. Lipid-lowering therapy does not reduce all-cause mortality or cardiovascular (CV) mortality. Lipoproteins play a role in the innate immune system. Our objective was to determine whether protection from infection might counterbalance adverse CV outcomes associated with lipoproteins. METHODS: We examined associations between serum apolipoprotein (Apo) A1, B, C2, C3, high-density lipoprotein and low-density lipoprotein (LDL) cholesterol and triglyceride levels and infectious mortality or hospitalization, CV mortality or hospitalization, and all-cause mortality in 433 prevalent HD patients. Cox models with time-varying apolipoprotein concentrations collected every 6 months for up to 2 years were used for analyses. RESULTS: Median follow-up time for all-cause mortality was 2.7 years (25th-75th percentile range: 2.2-3.4 years). One hundred seventy-nine (41%) patients had an infection-related event. In multivariable models, higher Apo B and LDL were associated with lower risks of infection-related outcomes (hazard ratio Apo B 0.92 [95% confidence interval 0.86-0.99 per 10 mg/dL, P = .03]; hazard ratio LDL 0.93 [95% confidence interval 0.87-1.00 per 10 mg/dL, P = .05]). Sixty-three (15%) participants had a CV-related event. No significant associations were observed between lipoproteins and CV outcomes. Eighty-seven (20%) participants died. Higher Apo A1, Apo B, and Apo C3 were associated with lower risks of all-cause mortality. There was no interaction between the use of lipid-lowering medication and any of the outcomes. CONCLUSION: Associations of lipoproteins with lower risk of serious infection accompanied by no significant association with CV events may help to explain the paradoxical association between lipids and survival and lack of benefit of lipid-lowering therapies in HD.

[99] *Hamada T, Khalaf N, Yuan C et al.* **Statin use and pancreatic cancer risk in two prospective cohort studies**. Journal of gastroenterology 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29362938

ABSTRACT

BACKGROUND: Statins, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, are common lipid-lowering agents and may reduce the risk of several cancer types including pancreatic cancer. However, the association between statin use and pancreatic cancer risk has not been fully evaluated in prospective studies. METHODS: We studied the association between statin use and incident pancreatic cancer in 113,059 participants from the prospective Nurses' Health Study and Health Professionals Follow-up Study. Statin use was self-reported via study questionnaires and updated biennially. Hazard ratios (HRs) and 95% confidence intervals (CIs) for incidence of pancreatic cancer were estimated using multivariable Cox proportional hazards models with adjustment for potential confounders. RESULTS: In total, 583 participants developed incident pancreatic cancer during 1.4 million person-years of follow-up. No difference was identified in pancreatic cancer risk for regular versus non-regular statin users (multivariable-adjusted HR 0.98; 95% CI 0.82-1.16). There was no significant heterogeneity in the association of statin use with pancreatic cancer risk between the cohorts. Similarly, longer duration of regular statin use was not associated with decreased risk of pancreatic cancer (Ptrend = 0.65). The results remained similar when we examined statin use status at baseline or accounting for 4-year latency period. We observed no statistically significant effect modification

for the association of statin use with pancreatic cancer risk by body mass index, smoking status, or diabetes mellitus status (all Pinteraction > 0.21). CONCLUSIONS: Regular statin use was not associated with pancreatic cancer risk in two large prospective cohort studies in the U.S.

[100] *Wu F, Luo T, Mei Y et al.* **Simvastatin alters M1/M2 polarization of murine BV2 microglia via Notch signaling**. Journal of neuroimmunology 2017.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29361314
ABSTRACT
Microglia play a critical role in the regulation of CNS immune function, which can be greatly affected by M1/M2 polarization. The role of Notch signaling in Statins induced alteration of M1/M2 polarization in BV2 cells was assessed in this study. M1 markers in LPS and Jagged-1 treated group were significantly increased and such increase was attenuated by simvastatin; however, M2 markers were enhanced. Moreover, simvastatin enhance the expression of Notch signaling molecules, and its regulatory effects were blocked in Notch1 knocked down cells. In conclusion, these findings indicated that simvastatin alters M1/M2 polarization of murine BV2 microglia via Notch signaling.

[101] *Chen J, Guo Y, Gui Y, Xu D*. **Physical exercise, gut, gut microbiota, and atherosclerotic cardiovascular diseases**. Lipids in health and disease 2018; 17:17.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29357881
ABSTRACT
Arteriosclerotic cardiovascular diseases (ASCVDs) are the leading cause of morbidity and mortality worldwide and its risk can be independently decreased by regular physical activity. Recently, ASCVD and its risk factors were found to be impacted by the gut microbiota through its diversity, distribution and metabolites. Meanwhile, several experiments demonstrated the relationship between physical exercise and diversity, distribution, metabolite of the gut microbiota as well as its functions on the lipid metabolism and chronic systematic inflammation. In this review, we summarize the current knowledge on the effects of physical exercise on ASCVD through modulation of the gut microbiota and intestinal function.

[102] *Esteve-Valverde E, Ferrer-Oliveras R, Gil-Aliberas N et al.* **Pravastatin for Preventing and Treating Preeclampsia: A Systematic Review**. Obstetrical & gynecological survey 2018; 73:40-55.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29368790
ABSTRACT
Importance: We have performed a systematic search to summarize the role of statins for preventing and treating severe preeclampsia. Objective: The aim of this study was to examine whether pravastatin is a useful and safe alternative for treating preeclampsia during pregnancy. Evidence Acquisition: A systematic MEDLINE (PubMed) search was performed (1979 to June 2017), which was restricted to articles published in English, using the relevant key words of "statins," "pregnancy," "preeclampsia," "obstetrical antiphospholipid syndrome," and "teratogenicity." Results: The initial search provided 296 articles. Finally, 146 articles were related to the use of statins during pregnancy, regarding their effect on the fetus and the treatment of preeclampsia. Ten studies were related to in vitro studies, 25 in animals, and 24 in

humans (13 case report series and 11 cohort studies). We found 84 studies on reviews of such guidelines on cardiovascular disease (35 studies), use of statins in the antiphospholipid syndrome (25 studies), statin's specific use during pregnancy (13 studies), or preeclampsia treatment (11 studies). Conclusions: Although the studies are of poor quality, the rate of major congenital abnormalities in the newborn exposed to statins during pregnancy is no higher than the expected when compared with overall risk population. The review shows a potential beneficial role of statins in preventing and treating severe preeclampsia that needs to be evaluated through well-designed clinical trials. Relevance: This update could influence positively the clinical practice, giving an alternative therapy for clinicians who treat preeclampsia, particularly in severe cases.

[103] *Mark L, Harangi M, Paragh G*. **[The labyrinth of residual risk: reduction of the remaining lipid and inflammation risk in the prevention of atherosclerosis]**. Orvosi hetilap 2018; 159:124-130.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29353502
ABSTRACT
Since cardiovascular diseases are the main cause of mortality worldwide, the reduction of their risk is a crucial point of present-day medicine. It has been proven unequivocally that the administration of various treatments has a favorable effect on the frequency of cardiovascular events and on the atherosclerosis leading to them. Although systematic and guideline-driven administration of these drugs has led to a decrease in the incidence and mortality of vascular events, the leading position of this group of diseases in mortality and morbidity has not changed. That is why medicine, besides keeping up actual guidelines optimally, is always searching for new modalities to further decrease residual risk. This residual risk can be diverse. The present paper summarizes the possibilities of reducing residual lipid and residual inflammatory risk after treatment according to the guidelines. It has been proven that lowering LDL-cholesterol below 1.8 mmol/l has a further advantage on the occurrence of vascular events. Treating the elevated lipoprotein(a), triglyceride and low HDL-cholesterol levels should decrease the residual lipid risk. Statins and statin-ezetimibe combination, besides lipid modulation, have an anti-inflammatory effect proved by C-reactive protein level reduction. Canakinumab has solely inflammation reducing effect through the inhibition of interleukin-1beta. It was administered subcutaneously once in 3 months in a large-scale clinical study and it has shown a 15% reduction in non-fatal myocardial infarction, non-fatal stroke and cardiovascular death, which opens new horizons in the anti-inflammatory treatment of atherosclerosis. Orv Hetil. 2018; 159(4): 124-130.

[104] *Zodda D, Giammona R, Schifilliti S*. **Treatment Strategy for Dyslipidemia in Cardiovascular Disease Prevention: Focus on Old and New Drugs**. Pharmacy (Basel, Switzerland) 2018; 6.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29361723
ABSTRACT
Prevention and treatment of dyslipidemia should be considered as an integral part of individual cardiovascular prevention interventions, which should be addressed primarily to those at higher risk who benefit most. To date, statins remain the first-choice therapy, as they have been shown to reduce the risk of major vascular events by lowering low-density lipoprotein

cholesterol (LDL-C). However, due to adherence to statin therapy or statin resistance, many patients do not reach LDL-C target levels. Ezetimibe, fibrates, and nicotinic acid represent the second-choice drugs to be used in combination with statins if lipid targets cannot be reached. In addition, anti-PCSK9 drugs (evolocumab and alirocumab) provide an effective solution for patients with familial hypercholesterolemia (FH) and statin intolerance at very high cardiovascular risk. Recently, studies demonstrated the effects of two novel lipid-lowering agents (lomitapide and mipomersen) for the management of homozygous FH by decreasing LDL-C values and reducing cardiovascular events. However, the costs for these new therapies made the cost-effectiveness debate more complicated.

[105] *Singh P, Zhang Y, Sharma P et al.* **Statins decrease leptin expression in human white adipocytes**. Physiological reports 2018; 6.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29372612
ABSTRACT
Statin use is associated with increased calorie intake and consequent weight gain. It is speculated that statin-dependent improvements in lipid profile may undermine the perceived need to follow lipid-lowering and other dietary recommendations leading consequently to increased calorie intake. However, increases in calorie intake in statin users may also be related to statin-dependent decreases in satiety factors such as leptin, an adipocyte-derived adipokine. The objective of our study was to examine the direct effects of statins on leptin expression. Adipocytes are the main source of circulating leptin. Therefore, we examined the effects of atorvastatin and simvastatin on leptin expression in cultured human white adipocytes. We show that treatment of white adipocytes with simvastatin and atorvastatin decreases leptin mRNA expression (simvastatin: P = 0.008, atorvastatin: P = 0.03) and leptin secretion (simvastatin: P = 0.0001, atorvastatin: P = 0.0001). Both simvastatin and atorvastatin mediate decreases in leptin expression via extracellular-signal-regulated kinases 1/2 and peroxisome proliferator-activated receptor gamma pathways (simvastatin: P = 0.01, atorvastatin: P = 0.026). Additionally, statin treatment also induced expected increases in adiponectin, while decreasing monocyte chemoattractant protein 1 (MCP1) mRNA. Furthermore, statins increased secretion of both total as well as high molecular weight adiponectin while decreasing MCP1 secretion. To conclude, statins act directly on human white adipocytes to regulate adipokine secretion and decrease leptin expression. Leptin is an important satiety factor. Hence, statin-dependent decreases in leptin may contribute, at least in part, to increases in food intake in statin users.

[106] *Baker MA, Nandivada P, Mitchell PD et al.* **Pretreatment with intravenous fish oil reduces hepatic ischemia reperfusion injury in a murine model**. Surgery 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29358007
ABSTRACT
BACKGROUND: Ischemia reperfusion injury is a barrier to liver surgery and transplantation, particularly for steatotic livers. The purpose of this study was to determine if pretreatment with a single dose of intravenous fish oil decreases hepatic ischemia reperfusion injury and improves recovery of injured livers. METHODS: Sixty adult male C57BL/6 mice received 1 g/kg intravenous fish oil (Omegaven, Fresenius Kabi) or isovolumetric 0.9% NaCl (saline) via tail vein 1 hour before 30 minutes of 70% hepatic ischemia. Animals were killed 4, 8, or 24 hours

postreperfusion, and livers were harvested for histologic analysis. RESULTS: Four hours postreperfusion, saline-treated livers demonstrated marked ischemia diffusely around the central veins, while intravenous fish oil-treated livers demonstrated only patchy necrosis with intervening normal parenchyma. Eight hours postreperfusion, all livers demonstrated pale areas of cell loss with surrounding regenerating hepatocytes. Ki67 staining confirmed 14.4/10 high-powered field (95% confidence interval, 3.2-25.6) more regenerating hepatocytes around areas of necrosis in intravenous fish oil-treated livers. Twenty-four hours postreperfusion, all livers demonstrated patchy areas of necrosis, with an 89% (95% confidence interval, 85-92) decrease in the area of necrosis in intravenous fish oil-treated livers. CONCLUSION: Intravenous fish oil treatment prior to hepatic ischemia reperfusion injury decreased the area of hepatic necrosis and increased hepatocyte regeneration compared to saline treatment in a mouse model.

[107] *Uchiyama H, Tsujimoto M, Shimada N et al.* **Evaluation of Trace Elements in Augmentation of Statin-Induced Cytotoxicity in Uremic Serum-Exposed Human Rhabdomyosarcoma Cells**. Toxins 2018; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29370118
ABSTRACT
Patients with end-stage kidney disease (ESKD) are at higher risk for rhabdomyolysis induced by statin than patients with normal kidney function. Previously, we showed that this increase in the severity of statin-induced rhabdomyolysis was partly due to uremic toxins. However, changes in the quantity of various trace elements in ESKD patients likely contribute as well. The purpose of this study is to determine the effect of trace elements on statin-induced toxicity in rhabdomyosarcoma cells exposed to uremic serum (US cells) for a long time. Cell viability, apoptosis, mRNA expression, and intracellular trace elements were assessed by viability assays, flow cytometry, real-time RT-PCR, and ICP-MS, respectively. US cells exhibited greater simvastatin-induced cytotoxicity than cells long-time exposed with normal serum (NS cells) (non-overlapping 95% confidence intervals). Intracellular levels of Mg, Mn, Cu, and Zn were significantly less in US cells compared to that in NS cells ($p < 0.05$ or 0.01). Pre-treatment with TPEN increased simvastatin-induced cytotoxicity and eliminated the distinction between both cells of simvastatin-induced cytotoxicity. These results suggest that Zn deficiencies may be involved in the increased risk for muscle complaints in ESKD patients. In conclusion, the increased severity of statin-induced rhabdomyolysis in ESKD patients may be partly due to trace elements deficiencies.