Literature update week 05 (2020)

[1] *Kanthi Y, de la Zerda A, Smith BR*. **Nanotherapeutic Shots through the Heart of Plaque**. ACS nano 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31986012
ABSTRACT
The past several decades have brought significant advances in the application of clinical and preclinical nanoparticulate drugs in the field of cancer, but nanodrug development in cardiovascular disease has lagged in comparison. Improved understanding of the spatiotemporal kinetics of nanoparticle delivery to atherosclerotic plaques is required to optimize preclinical nanodrug delivery and to drive their clinical translation. Mechanistic studies using super-resolution and correlative light microscopy/electron microscopy permit a broad, ultra-high-resolution picture of how endothelial barrier integrity impacts the enhanced permeation and retention (EPR) effect for nanoparticles as a function of both atherosclerosis progression and metabolic therapy. Studies by Beldman et al. in the December issue of ACS Nano suggest atherosclerotic plaque progression supports endothelial junction stabilization, which can reduce nanoparticle entry into plaques, and metabolic therapy may induce similar effects. Herein, we examine the potential for advanced dynamic intravital microscopy-based mechanistic studies of nanoparticle entry into atherosclerotic plaques to shed light on the advantages of free extravasation versus immune-mediated nanoparticle uptake for effective clinical translation. We further explore the potential combination of metabolic therapy with another emerging cardiovascular disease treatment paradigm-efferocytosis stimulation-to enhance atherosclerotic plaque regression.

[2] *Roberts CS, Stoler RC, Roberts WC*. **The Case for Primary Prevention of Atherosclerotic Events from Study of a Single Patient**. The American journal of cardiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32005440
ABSTRACT
This report describes a 64-year-old woman who presented with unstable angina pectoris, her first atherosclerotic event, and who underwent coronary bypass including endarterectomy of the entire right coronary artery which was diffusely and severely narrowed by atherosclerotic plaque. Preoperatively, she fulfilled none of the present-day criteria for lipid-lowering drug therapy. The report demonstrates the deficiency of present-day lipid-lowering drug guidelines and emphasizes the need to switch emphasis from decreasing risk of an atherosclerotic event to the prevention of arterial plaques, a goal which will require a much lower threshold of low-density lipoprotein cholesterol to initiate drug therapy.

[3] *Goldberg IJ, Sharma G, Fisher EA*. **Atherosclerosis: Making a U Turn**. Annual review of medicine 2020; 71:191-201.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31986087
ABSTRACT
The development of potent cholesterol-reducing medications in the last decade of the twentieth century has altered the approach to prevention and treatment of cardiovascular disease (CVD). Initial experience with statins, and more recently with the addition of PCSK9 inhibitors, has proven that human CVD, like that in animal models, can be halted and regressed. Available clinical data show that the lower the achieved level of low-density lipoprotein cholesterol, the greater the regression of disease. Investigative studies are now aimed to understand those factors that both accelerate and

impede this healing process. Some of these are likely to be modifiable, and the future of atherosclerotic CVD treatment is likely to be early screening, use of measures to repair atherosclerotic arteries, and prevention of most CVD events.

[4] *Healy A, Berus JM, Christensen JL et al.* **Statins Disrupt Macrophage Rac1 Regulation Leading to Increased Atherosclerotic Plaque Calcification**. Arteriosclerosis, thrombosis, and vascular biology 2020:Atvbaha119313832.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31996022
ABSTRACT
OBJECTIVE: Calcification of atherosclerotic plaque is traditionally associated with increased cardiovascular event risk; however, recent studies have found increased calcium density to be associated with more stable disease. 3-hydroxy-3-methylglutaryl coenzymeA reductase inhibitors or statins reduce cardiovascular events. Invasive clinical studies have found that statins alter both the lipid and calcium composition of plaque but the molecular mechanisms of statin-mediated effects on plaque calcium composition remain unclear. We recently defined a macrophage Rac-IL-1beta (interleukin-1 beta) signaling axis to be a key mechanism in promoting atherosclerotic calcification and sought to define the impact of statin therapy on this pathway. Approach and Results: Here, we demonstrate that statin therapy is independently associated with elevated coronary calcification in a high-risk patient population and that statins disrupt the complex between Rac1 and its inhibitor RhoGDI (Rho GDP-dissociation inhibitor), leading to increased active (GTP bound) Rac1 in primary monocytes/macrophages. Rac1 activation is prevented by rescue with the isoprenyl precursor geranylgeranyl diphosphate. Statin-treated macrophages exhibit increased activation of NF-kappaB (nuclear factor kappa-light-chain-enhancer of activated B cells), increased IL-1beta mRNA, and increased Rac1-dependent IL-1beta protein secretion in response to inflammasome stimulation. Using an animal model of calcific atherosclerosis, inclusion of statin in the atherogenic diet led to a myeloid Rac1-dependent increase in atherosclerotic calcification, which was associated with increased serum IL-1beta expression, increased plaque Rac1 activation, and increased plaque expression of the osteogenic markers, alkaline phosphatase, and RUNX2. CONCLUSIONS: Statins are capable of increasing atherosclerotic calcification through disinhibition of a macrophage Rac1-IL-1beta signaling axis.

[5] *Cesaro A, Bianconi V, Gragnano F et al.* **Beyond cholesterol metabolism: The pleiotropic effects of proprotein convertase subtilisin/kexin type 9 (PCSK9). Genetics, mutations, expression, and perspective for long-term inhibition**. Biofactors 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31999032
ABSTRACT
Proprotein convertase subtilisin/kexin type 9 (PCSK9) has a crucial role in lipid metabolism, particularly due to its function in low-density lipoprotein receptor degradation. Gain-of-function genetic mutations of PCSK9 result in autosomal dominant familial hypercholesterolemia, characterized by high levels of low-density lipoprotein cholesterol (LDL-C) and clinical signs of early atherosclerosis. In recent years, PCSK9 has become an important therapeutic target for cholesterol-lowering therapy. Particularly, its inhibition with monoclonal antibodies has shown excellent efficacy in decreasing LDL-C and reducing cardiovascular events. However, PCSK9, first identified in the brain, seems to be a ubiquitous protein with different tissue-specific functions also independent of cholesterol metabolism. Accordingly, it

appears to be involved in the immune response, haemostasis, glucose metabolism, neuronal survival, and several other biological functions. This review provides a comprehensive overview of the genetics, biochemical structure, expression, and function of PCSK9 and discusses the potential implications of its long-term pharmacological inhibition.

[6] *Wang H, Daggy BP*. **The Role of Fish Oil in Inflammatory Eye Diseases**. Biomedicine hub 2017; 2:1-12.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31988905
ABSTRACT
Consumption of fish oil is associated with reduced morbidity and mortality of cardiovascular diseases and also reduces the severity of many other inflammatory diseases and autoimmune disorders. The beneficial effects are attributed to the anti-inflammatory effects of the omega-3 polyunsaturated fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), found in fish oils. The mechanism of the anti-inflammatory effects was long thought to be by modulating the production of proinflammatory mediators, including prostaglandins, thromboxanes, and leukotrienes. Recent advances in research into the novel lipid mediators (resolvins, protectins, and maresins) derived from EPA and DHA and their role in the resolution of inflammation have shed new light on the pleiotropic nature of these fatty acids. In this review, we focus on the effects of EPA and DHA from fish oil in the treatment of two common inflammatory eye diseases - dry eye disease and age-related macular degeneration. Evidence from recent studies lends support to a role of fish oil in the treatment of these two eye diseases.

[7] *Tanguturi VK, Kennedy KF, Virani SS et al.* **Association between poverty and appropriate statin prescription for the treatment of hyperlipidemia in the United States: An analysis from the ACC NCDR PINNACLE registry**. Cardiovascular revascularization medicine : including molecular interventions 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31992531
ABSTRACT
BACKGROUND: Poverty is associated with a higher risk of myocardial infarction and cardiac death, both of which are decreased by treatment of hyperlipidemia. There may be differences in the appropriate treatment of hyperlipidemia between richer and poorer Americans. In this study, we aimed to evaluate the association between income level and appropriate lipid-lowering therapy. METHODS: We identified outpatient visits in the National Cardiovascular Data Registry's Practice Innovation and Clinical Excellence (PINNACLE) Registry and determined appropriateness of lipid-lowering therapy among patients in different income quintiles (Quintile 5 being the highest income quintile). Logistic regression at the patient level was performed to evaluate the independent association of income and the primary outcome of appropriate statin therapy. The analysis was repeated before and after November 2013 given a change in guideline definitions. RESULTS: The study included 1,655,723 patients. Overall, 68-73% of patients were treated appropriately under the ATP III Guidelines and 57-62% of patients were treated appropriately under the ACC/AHA Guidelines. Patients in the wealthiest quintile had higher odds of appropriate statin therapy under both guidelines relative to patients in the poorest quintile (OR 1.06 [1.05-1.07] for ATP III and OR 1.03 [1.01-1.04] for ACC/AHA). In the whole sample, patients with higher estimated income had a small but significant increased likelihood of appropriate statin therapy (point-biserial correlation 0.035 [p<0.001] for ATP III and 0.026 [p<0.001] for ACC/AHA).

CONCLUSIONS: Here we describe a small association between appropriate statin use and income. Further investigation into barriers in the use of evidence-based therapies in poorer populations is needed.

[8] *Lee TI*. **In reply: How should diabetic dyslipidemia be treated?** Cleveland Clinic journal of medicine 2020; 87:11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31990648
ABSTRACT

[9] *Modarressi T*. **How should diabetic dyslipidemia be treated?** Cleveland Clinic journal of medicine 2020; 87:11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31990647
ABSTRACT

[10] *Govsyeyev N, Nehler MR, Hiatt WR, Bonaca MP*. **Tackling Elevated Risk in PAD: Focus on Antithrombotic and Lipid Therapy for PAD**. Current cardiology reports 2020; 22:13.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31997026
ABSTRACT
The PAD population is at increased risk of major adverse cardiovascular events (MACE) and major adverse limb events (MALE). Risk factor modification, symptom control, antithrombotic, and lipid therapies are the mainstays of PAD medical therapy. Recent data has challenged prior recommendations regarding the optimal secondary prevention strategies in PAD. PURPOSE OF REVIEW: To review clinical evidence from large randomized controlled trials showing the benefit of antithrombotic and lipid therapy in the PAD population. RECENT FINDINGS: The COMPASS trial challenged prior recommendations regarding anticoagulation in PAD. Among the PAD subgroup, rivaroxaban 2.5 mg plus aspirin reduced MACE (HR 0.72, 95% CI 0.57-0.90, p = 0.0047), MALE (HR 0.54, 95% CI 0.35-0.82, p = 0.0037), and major amputation (HR 0.30, 95% CI 0.11-0.80, p = 0.011) compared with aspirin monotherapy. The THEMIS trial showed a 55% risk reduction for MALE with ticagrelor DAPT compared with aspirin monotherapy (HR 0.45, 95% CI 0.23-0.86). The FOURIER trial revealed that lowering LDL cholesterol below current targets with a PCSK9 inhibitor reduced MACE (HR 0.73, 95% CI 0.59-0.91, p = 0.0040) and MALE (HR 0.43, 95% CI 0.19-0.99, p = 0.042) in subjects with symptomatic PAD. Recent high-quality evidence shows the benefit of antiplatelet therapy, anticoagulation therapy, and lipid therapy in reducing MACE and MALE in PAD. Despite these findings, implementation remains a challenge and focus should now shift towards adopting evidence-based recommendations in clinical practice.

[11] *Fattah TA, Saeed A, Shehzadi SA*. **Synthetic Approaches Towards Antihypercholesterolemic Drug Simvastatin**. Current organic synthesis 2019; 16:652-670.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31984887
ABSTRACT
Cardiovascular diseases are among the most threatening problems being faced by twenty-first century humans. The core cause of these diseases is high cholesterol level. Simvastatin (1: Synvinolin) is a well-known cholesterol-lowering drug marketed under the trade name Zocor(R), which significantly reduces the risk of cardiovascular diseases related to hypercholesterolemia and is effective in lowering the total

plasma cholesterol, low-density and very low-density lipoprotein cholesterol. It also enhances the high-density lipoprotein cholesterol. This review article aims to provide an overview of several chemical and biological methods utilized for the production of simvastatin in high yields and purity. Many robust and scalable methods have been described using lovastatin (2: Mevinolin) as a starting material, produced by the fungal strain of Aspergelius terreus. Enzymatic synthesis of simvastatin is also highlighted in this review. In addition, detailed experimental conditions, as well as the compatibility for industrial-scale preparations of simvastatin are also discussed.

[12] *Henein MY, Vancheri S, Bajraktari G, Vancheri F*. **Coronary Atherosclerosis Imaging**. Diagnostics (Basel, Switzerland) 2020; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31991633
ABSTRACT
Identifying patients at increased risk of coronary artery disease, before the atherosclerotic complications become clinically evident, is the aim of cardiovascular prevention. Imaging techniques provide direct assessment of coronary atherosclerotic burden and pathological characteristics of atherosclerotic lesions which may predict the progression of disease. Atherosclerosis imaging has been traditionally based on the evaluation of coronary luminal narrowing and stenosis. However, the degree of arterial obstruction is a poor predictor of subsequent acute events. More recent techniques focus on the high-resolution visualization of the arterial wall and the coronary plaques. Most acute coronary events are triggered by plaque rupture or erosion. Hence, atherosclerotic plaque imaging has generally focused on the detection of vulnerable plaque prone to rupture. However, atherosclerosis is a dynamic process and the plaque morphology and composition may change over time. Most vulnerable plaques undergo progressive transformation from high-risk to more stable and heavily calcified lesions, while others undergo subclinical rupture and healing. Although extensive plaque calcification is often associated with stable atherosclerosis, the extent of coronary artery calcification strongly correlates with the degree of atherosclerosis and with the rate of future cardiac events. Inflammation has a central role in atherogenesis, from plaque formation to rupture, hence in the development of acute coronary events. Morphologic plaque assessment, both invasive and non-invasive, gives limited information as to the current activity of the atherosclerotic disease. The addition of nuclear imaging, based on radioactive tracers targeted to the inflammatory components of the plaques, provides a highly sensitive assessment of coronary disease activity, thus distinguishing those patients who have stable disease from those with active plaque inflammation.

[13] *Abdelkawy KS, Abdelaziz RM, Abdelmageed AM et al.* **Effects of Green Tea Extract on Atorvastatin Pharmacokinetics in Healthy Volunteers**. European journal of drug metabolism and pharmacokinetics 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31997084
ABSTRACT
BACKGROUND AND OBJECTIVES: Green tea catechins were recently reported to inhibit drug transporters such as organic anion-transporting polypeptides (OATPs) and metabolic enzymes, affecting the bioavailability of many drugs. This study aimed to evaluate the clinical significance of the effects of different doses of green tea extract on the pharmacokinetic parameters of atorvastatin and to rationalize the associated interaction mechanism. METHODS: A randomized, double-blind, three-phase crossover study involving 12 healthy volunteers was performed. Participants received a single

dose of atorvastatin 40 mg alone (control group), atorvastatin 40 mg plus a capsule containing 300 mg of dry green tea extract, or atorvastatin 40 mg plus a capsule containing 600 mg of dry green tea extract. Plasma samples taken from the volunteers were analyzed for atorvastatin using liquid chromatography-tandom mass spectrometry (LC/MS/MS). RESULTS: Compared to atorvastatin alone, the administration of 300 mg or 600 mg of the green tea extract along with atorvastatin decreased the peak plasma concentration (Cmax) of atorvastatin by 25% and 24%, respectively ($P < 0.05$), and the area under the plasma concentration-time curve (AUC0-infinity) of atorvastatin by 24% and 22%, respectively ($P < 0.05$). Additionally, administration of 300 mg or 600 mg of the green tea extract increased the apparent oral clearance (CL/F) of atorvastatin by 31% and 29%, respectively. The time to Cmax (Tmax) and the elimination half-life (t1/2) of atorvastatin did not differ among the three phases. The effects of 600 mg of the green tea extract on the pharmacokinetic parameters of atorvastatin were not significantly different from the effects of 300 mg of the green tea extract. CONCLUSION: Green tea extract decreases the absorption but not the elimination of atorvastatin, possibly by inhibiting OATP, albeit not in a dose-dependent manner. Coadministration of green tea extract with atorvastatin may necessitate the monitoring of the plasma concentration of atorvastatin in clinical practice.

[14] *Amarenco P, Kim JS, Labreuche J et al.* **Treat stroke to target trial design: First trial comparing two LDL targets in patients with atherothrombotic strokes**. European stroke journal 2019; 4:271-280.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31984235

ABSTRACT

Background: In patients with non-cardio-embolic stroke, atorvastatin 80 mg/day reduced the relative risk of recurrent stroke by 16%, and a post hoc analysis showed that achieving an LDL-c of less than 70 mg/dL reduced the relative risk by 28% as compared to an on-treatment LDL of 100 mg/dL or more. Current guidelines from the French drug agency recommend treating with a statin after an ischaemic stroke to a target of less than 100 mg/dL, but no study directly tested LDL-c targets. The Treat Stroke to Target (TST) trial will compare the efficacy of achieving an LDL-c of less than 70 mg/dL versus an achieved LDL-c of 100 +/- 10 mg/dL for secondary prevention in patients with recent ischaemic stroke of atherosclerotic origin.Main hypothesis: An achieved on-treatment LDL-c of less than 70 mg/dL will reduce by 25% the risk of recurrent ischaemic stroke, myocardial infarction, urgent coronary or carotid revascularisation following new symptoms requiring hospitalisation, and vascular death compared with on-treatment LDL-c of 100 +/- 10 mg/dL. Design: Patients are randomised to either LDL-c levels, and the investigator who is not blinded can use the lipid-lowering agent of his/her choice available on the market (including statins and ezetimibe), in order to achieve the assigned LDL-c level. To be eligible for enrolment, patients have a recent ischaemic stroke or TIA of atherosclerotic origin with at least one arterial stenosis of a cerebral artery, enrolled between acute phase of the qualifying stroke (once the neurological deficit is stabilised) and three months. The initial planned sample size of 3760 participants followed three years was amended to allow follow-up of all enrolled patients until 385 primary efficacy outcome events have occurred, and no later than 31 December 2019. Patients will be recruited in 76 sites in two countries (France and South Korea) between March 2010 and December 2018 (last included patient followed up to one year). Safety outcomes will include haemorrhagic strokes and new onset diabetes. All primary endpoints will be adjudicated by an endpoint committee, blinded to the assigned LDL-c level. Two sub-studies assess (1) the relative effect of assigned LDL-c levels on occurrence of new atherosclerotic plaque as detected by carotid ultrasound during follow-up, using M'ATH software for repositioning and (2) the genetic and biomarker drivers of recurrent primary

endpoints according to assigned LDL-c lowering arm, in atherosclerotic strokes. Summary: The TST trial is evaluating the benefits of achieving an LDL-c less than 70 mg/dL for secondary stroke prevention in ischaemic stroke patients of atherosclerotic origin. Main results are anticipated in 2020 or earlier (ClinicalTrials.gov NCT01252875).

[15] *Batista-Gonzalez A, Vidal R, Criollo A, Carreno LJ*. **New Insights on the Role of Lipid Metabolism in the Metabolic Reprogramming of Macrophages**. Frontiers in immunology 2019; 10:2993.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31998297
ABSTRACT
Macrophage activation is intimately linked to metabolic reprogramming. Inflammatory (M1) macrophages are able to sustain inflammatory responses and to kill pathogens, mostly by relying on aerobic glycolysis and fatty acid biosynthesis. Glycolysis is a fast way of producing ATP, and fatty acids serve as precursors for the synthesis of inflammatory mediators. On the opposite side, anti-inflammatory (M2) macrophages mediate the resolution of inflammation and tissue repair, switching their metabolism to fatty acid oxidation and oxidative phosphorylation. Over the years, this classical view has been challenged by recent discoveries pointing to a more complex metabolic network during macrophage activation. Lipid metabolism plays a critical role in the activation of both M1 and M2 macrophages. Recent evidence shows that fatty acid oxidation is also essential for inflammasome activation in M1 macrophages, and glycolysis is now known to fuel fatty acid oxidation in M2 macrophages. Ultimately, targeting lipid metabolism in macrophages can improve the outcome of metabolic diseases. Here, we review the main aspects of macrophage immunometabolism from the perspective of the metabolism of lipids. Building a reliable metabolic network during macrophage activation will bring us closer to targeting macrophages for improving human health.

[16] *Heinicke V, Halle M*. **[Lifestyle intervention in the primary prevention of cardiovascular diseases]**. Herz 2020; 45:30-38.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31993680
ABSTRACT
Cardiovascular diseases are the leading cause of death worldwide. Adherence to a healthy lifestyle lifelong is capable of significantly reducing the cardiovascular risk by up to 70% and is therefore a key component in primary prevention of cardiovascular disease. According to the European and American guidelines lifestyle interventions include not smoking, daily physical activity of >/=150min/week at moderate intensity or 75min/week for higher intensity physical activity, a cardioprotective nutrition (high proportion of unsaturated fatty acids, low amounts of saturated fatty acids and low salt intake), normal body weight (body mass index 20-25kg/m(2)), arterial blood pressure <140/90mmHg (optimum <130/80mmHg), low-density lipoprotein (LDL)-cholesterol target values depending on the cardiovascular risk and a normal glucose metabolism in type 2 diabetes mellitus with adjustment of a HbA1c to <7%. Lifestyle measures with weight reduction and intensification of physical activity can improve the cardiometabolic risk factors. In this way reduction of the systolic and diastolic blood pressures by approximately 10-15mmHg, reduction of HbA1c by approximately 1% and reduction of triglycerides by ca. 30-40% are possible. The LDL-cholesterol and lipoprotein(a) levels cannot be easily influenced. Beyond the recommendations for a cardioprotective lifestyle, additional pharmacological therapy may have to be added depending on the cardiovascular risk profile.

[17] *Nixdorff U*. **[Meaningful diagnostics: imaging]**. Herz 2020; 45:17-23.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32002564
ABSTRACT
Imaging of subclinical atherosclerosis is an integrated component of a preventive medicine algorithm; i.e. on the basis of a cardiovascular risk stratification patients with a low and intermediate risk qualify for further imaging (cave: Bayes' theorem). Imaging procedures for subclinical atherosclerosis have one thing in common: atherosclerosis is detected and localized directly, for which cardiac multidetector computed tomography (MDCT; coronary calcium scoring, CACS) and vascular ultrasound (carotid and/or femoral arteries) are used to measure the plaque burden. The result is viewed as a risk modifier. The risk assessment is not related to symptoms. In addition to the detection and localization of atherosclerosis this also enables assessment of the "risk age" according to the tables of the European Society of Cardiology (ESC) and even the biological age, which can be estimated based on nomograms. This knowledge can be used to promote patient compliance and adherence to medication.

[18] *Moroi M, Nagayama D, Hara F et al.* **Outcome of pitavastatin versus atorvastatin therapy in patients with hypercholesterolemia at high risk for atherosclerotic cardiovascular disease**. International journal of cardiology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31987664
ABSTRACT
BACKGROUND: There has been no report about outcome of pitavastatin versus atorvastatin therapy in high-risk patients with hypercholesterolemia. METHODS: Hypercholesterolemic patients with one or more risk factors for atherosclerotic diseases (n = 664, age = 65, male = 54%, diabetes = 76%, primary prevention = 74%) were randomized to receive pitavastatin 2 mg/day (n = 332) or atorvastatin 10 mg/day (n = 332). Follow-up period was 240 weeks. The primary end point was a composite of cardiovascular death, sudden death of unknown origin, nonfatal myocardial infarction, nonfatal stroke, transient ischemic attack, or heart failure requiring hospitalization. The secondary end point was a composite of the primary end point plus clinically indicated coronary revascularization for stable angina. RESULTS: The mean low-density lipoprotein cholesterol (LDL-C) level at baseline was 149 mg/dL. The mean LDL-C levels at 1 year were 95 mg/dL in the pitavastatin group and 94 mg/dL in the atorvastatin group. There were no differences in LDL-C levels between both groups, however, pitavastatin significantly reduced the risk of the primary end point, compared to atorvastatin (pitavastatin = 2.9% and atorvastatin = 8.1%, HR, 0.366; 95% CI 0.170-0.787; P = 0.01 by multivariate Cox regression) as well as the risk of the secondary end point (pitavastatin = 4.5% and atorvastatin = 12.9%, HR = 0.350; 95%CI = 0.189-0.645, P = 0.001). The results for the primary and secondary end points were consistent across several prespecified subgroups. There were no differences in incidence of adverse events between the statins. CONCLUSION: Pitavastatin therapy compared with atorvastatin more may prevent cardiovascular events in hypercholesterolemic patients with one or more risk factors for atherosclerotic diseases despite similar effects on LDL-C levels.

[19] *Shaker DS, Ishak RAH, Elhuoni MA, Ghoneim AM*. **Boosting transdermal delivery of atorvastatin calcium via o/w nanoemulsifying system: Two-step optimization, ex vivo and in vivo evaluation**. Int J Pharm 2020; 578:119073.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31982556

ABSTRACT
A nanoemulsion system was designed for Atorvastatin calcium (ATOR) transdermal delivery to overcome its poor bioavailability of (30%) resulting from the extensive first-pass effect and dissolution rate-limited in vivo absorption. Pseudo ternary phase diagrams were developed, and various NE formulae were prepared using oleic acid (OA), Tween 80 as surfactant and PEG 400 as cosurfactant, ethanol and limonene as permeation enhancers (PEs). NEs were characterized for morphology, droplet size, zeta potential and in vitro release. The optimized formulae were assessed for ex vivo transdermal permeation and in vivo pharmacodynamic/pharmacokinetic studies. Hypocholesterolemic effect after 7 days skin treatment was detected and compared to oral ATOR dispersion. Finally, blood plasma levels were measured for 24 h for rats received the selected transdermal NE and transdermal drug in OA. The obtained results suggested the low potentiality of NE systems in transdermal delivery of lipophilic drugs, only the addition of PEs is driving factor for increasing drug flux through full thickness rat skin. In the optimized formula, the presence of ethanol and PEG 400 disrupts SC lipids exhibiting rapid ex vivo release profile compared to other NEs and to ATOR in OA. In contrast, the optimized NE achieved a prolonged plasma profile. Transdermal NE was significantly more efficient than oral administration in lowering cholesterol plasma level and in increasing ATOR bioavailability. In conclusion, data revealed no correlation between ex vivo and in vivo studies explained by the collapse of the follicles in ex vivo skin permeation study, leaving only the lipoidal pathway for NE to pass through, thus only NE components, neither nanosizing nor other reported mechanisms, are the main influencing factors. In vivo experiments suggested that o/w NE changed ATOR pathway to follicular delivery leading to accumulation of NE in follicles and consequently a prolonged plasma profile.

[20] *Kim W, Chang K, Cho EJ et al.* **A randomized, double-blind clinical trial to evaluate the efficacy and safety of a fixed-dose combination of amlodipine/rosuvastatin in patients with dyslipidemia and hypertension**. Journal of clinical hypertension (Greenwich, Conn.) 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32003938

ABSTRACT
This multicenter, randomized, double-blind, parallel-group phase III clinical trial aimed to investigate the efficacy and safety of a rosuvastatin + amlodipine combination compared with that of rosuvastatin or amlodipine monotherapy in hypertensive patients with dyslipidemia. A total of 106 patients of 15 institutions in Korea were randomly assigned to 1 of 3 treatment groups: rosuvastatin 20 mg + amlodipine 10 mg, amlodipine 10 mg, or rosuvastatin 20 mg. After 8 weeks of treatment, the mean +/- SD of change in mean sitting systolic blood pressure (msSBP) was -22.82 +/- 12.99 mm Hg in the rosuvastatin + amlodipine group, the most decreased among the treatment groups. The percentage of patients whose msSBP decreased >/=20 mm Hg or msDBP decreased >/=10 mm Hg was also highest in this group (74.29%). The mean +/- SD percentage change in low-density lipoprotein cholesterol (LDL-C) level from baseline after 8 weeks was -52.53% +/- 11.21% in the rosuvastatin + amlodipine group, the most decreased among the treatment groups. More patients in the rosuvastatin + amlodipine group achieved their target LDL-C goal at 8 weeks, compared with the other treatment groups (97.14%). No serious adverse events or adverse drug reactions were observed in all groups. In hypertensive patients with dyslipidemia, combination treatment with rosuvastatin 20 mg + amlodipine 10 mg effectively reduced blood pressure and LDL-C levels while maintaining safety.

[21] *Sofogianni A, Tziomalos K*. **Fixed-dose combinations of lipid-lowering and antihypertensive agents: The way forward?** Journal of clinical hypertension (Greenwich, Conn.) 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32003930
ABSTRACT

[22] *Pires Borges IB, de Oliveira DS, Misse RG et al.* **Safety of Atorvastatin in Patients With Stable Systemic Autoimmune Myopathies: A Pilot Prospective Study**. Journal of clinical rheumatology : practical reports on rheumatic & musculoskeletal diseases 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31985725
ABSTRACT
BACKGROUND/OBJECTIVE: Patients with systemic autoimmune myopathies (SAMs) have high prevalence of dyslipidemia and, consequently, possible endothelial dysfunction and vascular stiffness. Our objective was to evaluate the possible benefits on endothelial function and vascular stiffness, as well as adverse effects of atorvastatin in SAMs. METHODS: A pilot longitudinal, double-blind, randomized, placebo-controlled study was conducted. Twenty-four of 242 patients were randomized at a 2:1 ratio to receive atorvastatin (20 mg/d) or placebo for a period of 12 weeks. Demographic data, comorbidities, and clinical and laboratory parameters, as well as endothelial function and arterial stiffness, were evaluated. RESULTS: Of the 24 randomized patients, 4 patients were excluded, with remaining 20 patients (14 in the atorvastatin group and 6 in the placebo group). The mean age of the patients was 49.0 years, and 75% of the patients were female. At baseline, the demographic data, disease status, treatment, cardiovascular comorbidities, and risk factors were comparable between the atorvastatin and placebo groups. After 12 weeks of follow-up of atorvastatin therapy, no improvements were observed for endothelial function and arterial stiffness in either group ($p > 0.05$). As expected, a significant reduction in total and low-density lipoprotein cholesterol levels was observed. During the study, no clinical intercurrences or disease relapses were observed in either group. CONCLUSIONS: The atorvastatin drug attenuated low-density lipoprotein cholesterol without worsening clinical outcomes in SAMs. No change was observed for endothelial function and arterial stiffness. Additional studies, with long-term follow-up time and different atorvastatin dosage, are needed to corroborate the results of this study.

[23] *Sharma P, Timilsina B, Adhikari J et al.* **Statin-induced necrotizing autoimmune myopathy: an extremely rare adverse effect from statin use**. Journal of community hospital internal medicine perspectives 2019; 9:503-506.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32002159
ABSTRACT
Statins are widely prescribed medications to prevent cardiovascular events. While self-limited statin myopathy is relatively common, statin-induced necrotizing autoimmune myopathy (SINAM) is extremely uncommon, with incidence of two cases per million per year. We present a case of SINAM after a decade of atorvastatin use, leading to debilitating weakness. A 71-year-old male presented with recurrent falls due to extreme bilateral lower-extremity weakness without pain or sensory changes. No fever, chills, rash, joint pain, recent infection or medication changes were reported. Reported taking atorvastatin 80 mg daily for 10 years. Physical examination revealed significant muscle wasting on right deltoid and proximal muscle weakness in all extremities. Lab tests included elevated creatinine kinase, aldolase, ESR, CRP and transaminases. Anti-HMGCR antibody was significantly elevated. TSH, serum

protein electrophoresis and RPR were unremarkable. ANA, Anti-Jo-1, anti-Mi2, anti-SRP, anti-ds-DNA, anti-SSA and anti-SSB antibodies were negative. MRI of thigh revealed diffuse myositis. Electromyogram revealed an acute myopathic process. Muscle biopsy showed muscle necrosis and C5b-9 sarcolemmal deposits on non-necrotic fibers without rimmed vacuoles. He was diagnosed with SINAM. Statin was discontinued, and steroid, immunoglobulins and azathioprine were started with gradual improvement. Unlike the self-limiting statin myopathy, SINAM is more severe and is associated with significant proximal muscle weakness, markedly elevated CK and persistent symptoms despite statin discontinuation. Anti-HMGCR antibodies are present in 100% of cases. Immunosuppressants are the mainstay of treatment, and statin rechallenge should never be done in these cases. Although relatively rare, physicians should be cognizant of SINAM.

[24] *Garg A, Fazio S, Duell PB et al.* **Molecular Characterization of Familial Hypercholesterolemia in a North American Cohort**. Journal of the Endocrine Society 2020; 4:bvz015.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31993549
ABSTRACT
Background: Familial hypercholesterolemia (FH) confers a very high risk of premature cardiovascular disease and is commonly caused by mutations in low-density lipoprotein receptor (LDLR), apolipoprotein B (APOB), or proprotein convertase subtilisin/kexin type 9 (PCSK9) and very rarely in LDLR adaptor protein 1 (LDLRAP1) genes. Objective: To determine the prevalence of pathogenic mutations in the LDLR, APOB, and PCSK9 in a cohort of subjects who met Simon Broome criteria for FH and compare the clinical characteristics of mutation-positive and mutation-negative subjects. Methods: Ninety-three men and 107 women aged 19 to 80 years from lipid clinics in the United States and Canada participated. Demographic and historical data were collected, physical examination performed, and serum lipids/lipoproteins analyzed. Targeted sequencing analyses of LDLR and PCSK9 coding regions and exon 26 of APOB were performed followed by detection of LDLR deletions and duplications. Results: Disease-causing LDLR and APOB variants were identified in 114 and 6 subjects, respectively. Of the 58 LDLR variants, 8 were novel mutations. Compared with mutation-positive subjects, mutation-negative subjects were older (mean 49 years vs 57 years, respectively) and had a higher proportion of African Americans (1% vs 12.5%), higher prevalence of hypertension (21% vs 46%), and higher serum triglycerides (median 86 mg/dL vs 122 mg/dL) levels. Conclusions: LDLR mutations were the most common cause of heterozygous FH in this North American cohort. A strikingly high proportion of FH subjects (40%) lacked mutations in known culprit genes. Identification of underlying genetic and environmental factors in mutation-negative patients is important to further our understanding of the metabolic basis of FH and other forms of severe hypercholesterolemia.

[25] *Wang D, Gao C, Xu X et al.* **Treatment of chronic subdural hematoma with atorvastatin combined with low-dose dexamethasone: phase II randomized proof-of-concept clinical trial**. Journal of neurosurgery 2020:1-9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32005012
ABSTRACT
OBJECTIVE: The authors sought to test the hypothesis that adding dexamethasone (DXM) to atorvastatin (ATO) potentiates the effects of ATO on chronic subdural hematoma (CSDH). METHODS: Sixty patients with CSDH underwent 5 weeks of treatment with an additional 7-week follow-up. Patients were randomized to receive a 5-week regimen of ATO 20 mg daily or ATO 20 mg daily plus a

DXM regimen (ATO+DXM). The 5-week DXM regimen was 2.25 mg daily for 2 consecutive weeks, followed by 0.75 mg twice daily for 2 weeks and 0.75 mg once daily for 1 week. The primary endpoint was hematoma reduction assessed by neuroimaging at baseline and at 5 weeks of follow-up. Secondary outcomes included neurological improvement assessed by using the Markwalder's Grading Scale and Glasgow Coma Scale (MGS-GCS). RESULTS: The mean patient age was 66.6 years, and 25% of patients were women. The patients who were treated with ATO+DXM had more obvious hematoma reduction at the 5th week (between-groups difference 18.37 ml; 95% CI 8.17-28.57; p = 0.0005). This reduction started from the 2nd week (14.51 ml; 95% CI 4.31-24.71; p = 0.0056) of treatment and persisted until the 12th week (17.50 ml; 95% CI 7.30-27.70; p = 0.0009). Complete recovery of neurological function (MGS-GCS grade 0) at 5 weeks was achieved in 83.33% and 32.14% of patients in the ATO+DXM and ATO groups, respectively. At the 5th week, patients receiving ATO+DXM had significantly lower levels of T cells and higher levels of regulatory T cells and endothelial progenitor cells in their peripheral blood. CONCLUSIONS: ATO+DXM was more effective than ATO alone in reducing hematoma and improving neurological function in patients with CSDH. These results require further confirmation in a randomized placebo-controlled trial.Clinical trial registration no.: ChiCTR-IPR-14005573 (http://www.chictr.org.cn/index.aspx).

[26] *Willemsen L, de Winther MPJ*. **Macrophage subsets in atherosclerosis as defined by single-cell technologies**. The Journal of pathology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32003464
ABSTRACT
Macrophages play a major role in the pathogenesis of atherosclerosis. Many studies have shone light on the different phenotypes and functions that macrophages can acquire upon exposure to local cues. The microenvironment of the atherosclerotic plaque contains a plethora of macrophage controlling factors, such as cytokines, oxidized low-density lipoproteins, and cell debris. Previous research has determined macrophage function within the plaque mainly by using immunohistochemistry and bulk analysis. The recent development and rapid progress of single-cell technologies like cytometry by time of flight (CyTOF) and single-cell RNA sequencing (scRNAseq) now enable comprehensive mapping of the wide range of cell types and their phenotypes present in atherosclerotic plaques. In this review, we discuss recent advances applying these technologies in defining macrophage subsets residing in the atherosclerotic arterial wall of mice and men. Resulting from these studies, we describe three main macrophage subsets: resident-like, pro-inflammatory, and anti-inflammatory foamy TREM2(hi) macrophages which are found in both mouse and human atherosclerotic plaques. Furthermore, we discuss macrophage subset specific markers and functions. More insights into the characteristics and phenotype of immune cells within the atherosclerotic plaque may guide future clinical approaches to treat disease. This article is protected by copyright. All rights reserved.

[27] *Cestari RN, Caris JA, Rocha A et al.* **Plasma mevalonic acid exposure as a pharmacodynamic biomarker of fluvastatin/atorvastatin in healthy volunteers**. Journal of pharmaceutical and biomedical analysis 2020; 182:113128.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32004772
ABSTRACT
Fluvastatin and atorvastatin are inhibitors of hydroxy-methylglutaryl-CoA (HMG-CoA) reductase, the enzyme that converts HMG-CoA to mevalonic acid (MVA). The present study reports for the first time

the analysis of mevalonolactone (MVL) in plasma samples by UPLC-MS/MS as well as the use of MVA, analyzed as MVL, as a pharmacodynamics parameter of fluvastatin in multiple oral doses (20, 40 or 80mg/day for 7 days) and atorvastatin in a single oral dose (20, 40 or 80mg) in healthy female volunteers. this study presents the use of MVL exposure as a pharmacodynamics biomarker of fluvastatin in multiple oral doses (20, 40 or 80mg/day for 7 days) or atorvastatin in a single oral dose (20, 40 or 80mg) in healthy volunteers (n=30). The administration of multiple doses of fluvastatin (n=15) does not alter the values (geometric mean and 95 % CI) of AUC0-24h of MVL [72.00 (57.49-90.18) vs 65.57 (51.73-83.12) ngh/mL], but reduces AUC0-6h [15.33 (11.85-19.83) vs 8.15 (6.18-10.75) ngh/mL] by approximately 47 %, whereas single oral dose administration of atorvastatin (n=15) reduces both AUC0-24h [75.79 (65.10-88.24) vs 32.88 (27.05-39.96) ngh/mL] and AUC0-6h [17.07 (13.87-21.01) vs 7.01 (5.99-8.22) ngh/mL] values by approximately 57 % and 59 %, respectively. In conclusion, the data show that the plasma exposure of MVL represents a reliable pharmacodynamic parameter for PK-PD (pharmacokinetic-pharmacodynamic) studies of fluvastatin in multiple doses and atorvastatin in a single dose.

[28] *Shaposhnik, II, Genkel VV*. **[Pleiotropic effects of ezetimibe]**. Kardiologiia 2019; 59:12-17.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31995721
ABSTRACT
The article discusses in detail the question of the additional positive effects of ezetimibe in addition to direct hypolipidemic action. The data of experimental and clinical studies in which the effect of ezetimibe on carbohydrate metabolism, inflammation, endothelial dysfunction, and liver is studied. The article also discusses the results of clinical studies that examined the effect of ezetimibe on atherosclerotic plaque.

[29] *Bijl D, Hama R*. **Statins for Familial Hypercholesterolemia from Childhood**. The New England journal of medicine 2020; 382:487-488.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31995703
ABSTRACT

[30] *Luirink IK, Kusters DM, Hutten BA*. **Statins for Familial Hypercholesterolemia from Childhood. Reply**. The New England journal of medicine 2020; 382:488-489.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31995705
ABSTRACT

[31] *Murata Y, Kami M*. **Statins for Familial Hypercholesterolemia from Childhood**. The New England journal of medicine 2020; 382:488.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31995704
ABSTRACT

[32] *Hanindita MH, Widjaja NA, Irawan R et al.* **Impact of Intravenous Omega-3-Enriched Lipid Emulsion on Liver Enzyme and Triglyceride Serum Levels of Children Undergoing Gastrointestinal Surgery**. Pediatric gastroenterology, hepatology & nutrition 2020; 23:98-104.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31988880
ABSTRACT

Purpose: To investigate the impact of omega-3-enriched lipid emulsion (LE) on liver enzyme (aspartate transaminase [AST] and alanine aminotransferase [ALT]) and triglyceride (TG) levels of children undergoing gastrointestinal surgery. Methods: This experimental randomized controlled group pretest-posttest design study included 14 children who underwent gastrointestinal surgery due to duodenal atresia, jejunal atresia, esophageal atresia, and need for parenteral nutrition for a minimum of 3 days at RSUD Dr. Soetomo Surabaya between August 2018 and January 2019. These children were divided into two groups, those who received standard intravenous LE (medium-chain triglyceride [MCT]/long-chain triglyceride [LCT]) and those who received intravenous omega-3-enriched LE. Differences in AST, ALT, and TG levels were measured before surgery and 3 days after the administration of parenteral nutrition. Results: Liver enzyme and TG levels in each group did not differ significantly before versus 3 days after surgery. However, TG levels were significantly lower in the omega-3-enriched intravenous LE group (p=0.041) at 3 days after surgery, and statistically significant difference in changes in TG levels was noted at 3 days after surgery between MCT/LCT intravenous LE group and the omega-3-enriched intravenous LE group (p=0.008). Conclusion: The intravenous omega-3-enriched LE had a better TG-lowering effect than the MCT/LCT intravenous LE in children undergoing gastrointestinal surgery.

[33] *Liu C, Zhu J, Hai B et al.* **Single Intraosseous Injection of Simvastatin Promotes Endothelial Progenitor Cell Mobilization, Neovascularization, and Wound Healing in Diabetic Rats**. Plastic and reconstructive surgery 2020; 145:433-443.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31985637

ABSTRACT

BACKGROUND: This study explored the effect of a single local intraosseous application of a small dose of simvastatin on the wound healing process in type 1 diabetic rats and related mechanisms. METHODS: The authors chose the streptozotocin-induced type 1 diabetic rat to establish a full-thickness dermal wound using a 12-mm-diameter sterile disposable punch. The rats (n = 32) were divided randomly into four groups: (1) normal control rats, (2) type 1 diabetic rats with intraosseous injection of hydrogel vehicle, (3) type 1 diabetic rats with intraosseous injection of simvastatin (0.5 mg), and (4) type 1 diabetic rats with intragastric administration of simvastatin (20 mg/kg per day). Wound closure was followed by digital planimetry. Mobilization of endothelial progenitor cells into the circulatory system was studied using fluorescence-activated cell sorting. Neovascularization was analyzed with immunofluorescence histochemical staining. The relative levels of adiponectin and stromal cell-derived factor 1 (SDF-1) in serum, bone, and wound tissues were examined by enzyme-linked immunosorbent assay and Western blot. RESULTS: Diabetic rats exhibited impaired wound healing. Intraosseous administration of simvastatin accelerated wound healing beginning at day 4, and angiogenesis was more obvious than in the control group. Enzyme-linked immunosorbent assay revealed that adiponectin concentrations in the diabetic rats with intraosseous injection of hydrogel vehicle plus simvastatin 0.5-mg group were significantly higher compared with the diabetic rats with intraosseous injection of hydrogel vehicle group beginning at day 4. Intraosseous administration of simvastatin decreased the expression of adiponectin and SDF-1 in bone tissue but enhanced the expression of adiponectin in wounded skin. CONCLUSIONS: A single local intraosseous application of simvastatin promotes wound healing in type 1 diabetic rat. The underlying mechanisms may be attributed to the regulation of the adiponectin/SDF-1 pathway, which plays a pivotal role in endothelial progenitor cell mobilization and angiogenesis.

Literature update week 05 (2020)

[34] *Gonzalez-Juanatey JR, Tamargo J, Torres F et al.* **Pharmacodynamic study of the cardiovascular polypill. Is there any interaction among the monocomponents?** Revista espanola de cardiologia (English ed.) 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31983653

ABSTRACT
INTRODUCTION AND OBJECTIVES: To compare the pharmacodynamics of the CNIC polypill (atorvastatin 40mg/ramipril 10mg/aspirin 100mg) in terms of low-density lipoprotein cholesterol (LDL-C) and systolic blood pressure (SBP), with the corresponding reference products (atorvastatin and ramipril). METHODS: This was a multicenter, randomized, open-label, and parallel 3-arm study comparing the effect of the CNIC polypill vs ramipril 10mg and atorvastatin 40mg on SBP and LDL-C. The coprimary endpoints were differences in the adjusted mean 24-hour SBP (using ambulatory BP measurement) and LDL-C during the study period estimated using an ANCOVA model. RESULTS: Of the 241 patients included in the per protocol population, 84 received the CNIC polypill (group A), 84 atorvastatin (group B), and 73 ramipril (group C). SBP decreased from 139.3+/-12.5 to 133.2+/-12.9mmHg in group A and from 138.1+/-11.9 to 134.0+/-12.8mmHg in group C (baseline adjusted mean difference for the decrease in SBP was 1.77mmHg (90%CI, -0.5 to 4.0) in favor of group A, without reaching statistical significance. LDL-C was reduced by 33.9+/-21.6 and 29.2+/-25.8mg/dL in groups A and B, respectively (baseline adjusted mean difference for the decrease in LDL-C was 7.0% (90%CI, 1.5-12.4), a significantly greater decrease with the polypill). The 3 treatments were well tolerated. CONCLUSIONS: The results of this study rule out a negative effect on blood pressure of the interaction between the components of the CNIC polypill. The reduction in LDL-C was greater in the CNIC polypill group, suggesting a synergistic effect of the components.