Literature update week 36 (2019)

[1] *Vrablik M, Catapano AL, Wiklund O et al.* **Understanding the Patient Perception of Statin Experience: A Qualitative Study**. Adv Ther 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31482507
ABSTRACT
INTRODUCTION: Statin intolerance (SI) occurs in patients with dyslipidemia treated with statins. Statin-associated symptoms have been reported, but the overall patient experience is poorly understood. No instruments are available to collect this patient experience. Our aim is to develop a patient survey to define SI from the patient's perspective, inform clinical practice, and identify potential patient characteristics and barriers associated with discontinuing treatment when statin-related difficulties are encountered. METHODS: We conducted qualitative concept elicitation interviews with 65 patients across 12 European study sites. A semi-structured qualitative interview guide was developed based on literature review and clinician interviews. Concept elicitation interviews with patients were used to describe the patient experience and develop the conceptual framework for the survey. RESULTS: Symptoms experienced by patients included muscle and non-muscle-related pain and discomfort; other muscle-related symptoms; gastrointestinal, cardiovascular, cold-like, fatigue-related, and sensory and systems symptoms; mood changes; and cognitive and memory problems. Impacts included limitations on general physical functioning; physical activities; social functioning; emotional impacts; sleep disturbances; decreased productivity; and increased healthcare use. Conceptual framework elements to support survey goals include demographic and clinical characteristics, health information and beliefs, statin side-effect history, symptom severity, and impact severity. CONCLUSIONS: Symptoms and impacts described by patients showed a wider range of symptoms and impacts than usually discussed clinically. The patient survey is designed to capture information from patients who experience difficulties with statin therapy and may be useful in identifying patients who are at higher risk for giving up or discontinuing their treatment. FUNDING: Amgen Inc.

[2] *Stec DE, Gordon DM, Hipp JA et al.* **The loss of hepatic PPARalpha promotes inflammation and serum hyperlipidemia in diet-induced obesity**. American journal of physiology. Regulatory, integrative and comparative physiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31483154
ABSTRACT
Agonists for PPARalpha are used clinically to reduce triglycerides and improve high-density lipoprotein (HDL) cholesterol levels in patients with hyperlipidemia. Whether the mechanism of PPARalpha activation to lower serum lipids occurs in the liver or other tissues is unknown. To determine the function of hepatic PPARalpha on lipid profiles in diet-induced obese mice, we placed hepatocyte-specific PPARalpha knockout (Ppara(HepKO)) and wild-type (Ppara(fl/fl)) mice on a high-fat diet (HFD) or normal fat diet (NFD) for 12 weeks. There was no significant difference in weight gain, percent body fat mass, or percent body lean mass between the groups of mice in response to HFD or NFD. Interestingly, the Ppara(HepKO) mice on HFD had worsened hepatic inflammation and a significant shift in the pro-inflammatory M1 macrophage population. These changes were associated with higher hepatic fat mass and decreased hepatic lean mass in the Pparalpha(HepKO) on HFD, but not in NFD, as measured by Oil Red O and non-invasive EchoMRI analysis (31.1+ 2.8 vs. 20.2 + 1.5, 66.6 + 2.5 vs. 76.4 + 1.5 %, $P<0.05$). We did

find that this was related to significantly reduced peroxisomal gene function and lower plasma beta-hydroxybutyrate in the Ppara(HepKO) on HFD, indicative of reduced metabolism of fats in the liver. Together, these provoked higher plasma triglyceride and apolipoprotein B100 (ApoB100) levels in the Ppara(HepKO) mice compared to Ppara(fl/fl) on HFD. These data indicate that hepatic PPARalpha functions to control inflammation and liver triglyceride accumulation, which prevents hyperlipidemia.

[3] *Agrawal R, Majeed M, Attar BM et al.* **Effectiveness of bezafibrate and ursodeoxycholic acid in patients with primary biliary cholangitis: a meta-analysis of randomized controlled trials**. Annals of gastroenterology 2019; 32:489-497.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31474796
ABSTRACT
Background: Ursodeoxycholic acid (UDCA) and obeticholic acid are currently approved treatments for primary biliary cholangitis (PBC). Since some patients do not respond adequately to UDCA, other therapies, such as bezafibrate, have been developed. In this meta-analysis we evaluated the efficacy and safety of using both UDCA and bezafibrate in patients with an inadequate response to UDCA. Methods: We evaluated all randomized controlled trials comparing the combination of UDCA and bezafibrate with UDCA monotherapy. Standardized mean difference (SMD) was used to assess the treatment effect of combination therapy compared with UDCA alone. Results: Ten trials with a total of 369 patients were analyzed. UDCA and bezafibrate combination therapy was more effective than UDCA monotherapy in improving alanine aminotransferase (SMD -2.04, 95% confidence interval [CI] -3.30 to -0.79), alkaline phosphatase at both less than 12 months (SMD -3.63, 95%CI -6.43 to -0.84) and more than 12 months (SMD -2.33, 95%CI -4.03 to -0.63), gamma-glutamyltransferase (SMD -1.29, 95%CI -2.67 to 0.08), triglyceride (SMD -0.80, 95%CI -1.41 to -0.19), immunoglobulin M (SMD -1.48, 95%CI -2.39 to -0.56), and cholesterol (SMD -4.61, 95%CI -7.34 to -1.89). There was no difference between the 2 groups in bilirubin, aspartate aminotransferase or albumin. None of the adverse effects differed statistically between the 2 groups. Conclusion: UDCA and bezafibrate combined treatment is superior to UDCA alone in UDCA non-responders with regard to decreasing liver biochemistry markers, without any significant increase in side effects in patients with PBC.

[4] *Li DQ, Lv FF, Li ZC et al.* **Anti-atherosclerotic effects between a combined treatment with simvastatin plus hirudin and single simvastatin therapy in patients with early type 2 diabetes mellitus**. Annals of translational medicine 2019; 7:302.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31475172
ABSTRACT
Background: This study aimed to investigate the efficacy and safety of simvastatin plus hirudin in preventing atherosclerosis in the patients with early type 2 diabetes mellitus (T2DM). Methods: This was a 24-week, randomized, open-label and controlled study in which 150 outpatients initially diagnosed with T2DM were randomly assigned into either simvastatin (40 mg daily at night) plus hirudin (3 g thrice daily) group [combined group (CG) n=75] or simvastatin (40 mg once daily) group [monotherapy group (MG) n=75]. The therapeutic efficacy was evaluated by the score of carotid artery atherosclerosis, plaque size, peak systolic velocity

(PSV) and end-diastolic velocity (EDV) on carotid ultrasonography at three and six months after treatment. Logistic regression analysis was used to investigate the correlation between treatment and carotid atherosclerosis. Results: One hundred and thirty-one patients completed this study, and there were no significant differences in the dropout rate in the CG (14.67%) and the MG (10.67%). Significant difference was found in the incidence of adverse events in the CG compared with the MG (37.50% vs. 17.91%, P<0.05) due to the higher risk of hemorrhage (12.50% vs. 1.49%, P<0.05), which did not affect the treatment compliance. The efficacy of combined treatment was better than monotherapy in the enhancement of carotid artery atherosclerosis scores (P<0.01), the plaque thickness (P<0.05) and the change of PSV (P<0.05) and EDV (P<0.05) since three months after treatment, which maintained to the end of observation. In addition, hirudin treatment was able to independently predict the carotid artery atherosclerosis scores (beta=2.37, P<0.05), the plaque thickening (beta=3.51, P<0.01) and the change of PSV (beta=1.69, P<0.05) and EDV (beta=1.79, P<0.05). Conclusions: Combined use of simvastatin and hirudin is well tolerated and possesses better anti-atherosclerotic effects than simvastatin alone in patients with early T2DM.

[5] *Duell PB, Gidding SS, Andersen RL et al.* **Longitudinal low density lipoprotein cholesterol goal achievement and cardiovascular outcomes among adult patients with familial hypercholesterolemia: The CASCADE FH registry**. Atherosclerosis 2019; 289:85-93.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31487564

ABSTRACT

BACKGROUND AND AIMS: There are limited data from the US on outcomes of patients in specialty care for familial hypercholesterolemia (FH). METHODS: CASCADE FH Registry data were analyzed to assess longitudinal changes in medication usage, in low density lipoprotein cholesterol (LDL-C) levels, and the rate of major adverse cardiovascular events (MACE (myocardial infarction, coronary revascularization, stroke or transient ischemic attack) in adults with FH followed in US specialty clinics. RESULTS: The cohort consisted of 1900 individuals (61% women, 87% Caucasian), with mean age of 56+/-15 years, 37% prevalence of ASCVD at enrollment, mean pretreatment LDL-C 249+/-68mg/dl, mean enrollment LDL-C 145mg/dl and 93% taking lipid lowering therapy. Over follow up of 20+/-11 months, lipid lowering therapy use increased (mean decrease in LDL-C of 32mg/dl (p < 0.001)). Only 48% of participants achieved LDL-C < 100mg/dl and 22% achieved LDL-C < 70mg/dl; ASCVD at enrollment was associated with greater likelihood of goal achievement. MACE event rates were almost 6 times higher among patients with prior ASCVD compared to those without (4.6 vs 0.8/100 patient years). Also associated with incident MACE were markers of FH severity and conventional ASCVD risk factors. CONCLUSIONS: With care in FH specialized clinics, LDL-C decreased, but LDL-C persisted >100mg/dl in 52% of patients. High ASCVD event rates suggest that adults with FH warrant designation as having an ASCVD risk equivalent. Earlier and more aggressive therapy of FH is needed to prevent ASCVD events.

[6] *Hori M, Ohta N, Takahashi A et al.* **Impact of LDLR and PCSK9 pathogenic variants in Japanese heterozygous familial hypercholesterolemia patients**. Atherosclerosis 2019; 289:101-108.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31491741

ABSTRACT
BACKGROUND AND AIMS: More than 4970 variants in the low-density lipoprotein receptor (LDLR) gene and 350 variants in the proprotein convertase subtilisin/kexin 9 (PCSK9) gene have been reported in familial hypercholesterolemia (FH) patients. However, the effects of these variants on FH pathophysiology have not been fully clarified. We aimed to update the LDLR and PCSK9 variants in Japanese heterozygous FH (HeFH) patients and annotate their clinical significance for the genetic diagnosis of HeFH. METHODS: A genetic analysis of the LDLR and PCSK9 genes was performed in 801 clinically diagnosed HeFH patients. The association of the pathogenic variants with the clinical FH phenotype was examined. RESULTS: Pathogenic variants in the LDLR and PCSK9 genes were found in 46% (n=296) and 7.8% (n=51) of unrelated FH patients (n=650), respectively. The prevalence of Achilles tendon thickness was low (44%) in patients harbouring PCSK9 pathogenic variants. Furthermore, 17% of unrelated FH patients harboured one of five frequent LDLR pathogenic variants: c.1845+2T > C, c.1012T > A: p.(Cys338Ser), c.1297G > C: p.(Asp433His), c.1702C > G: p.(Leu568Val), and c.2431A > T: p.(Lys811*). Patients harbouring the c.1845+2T > C and c.1702C > G: p.(Leu568Val) variants had significantly lower serum LDL-cholesterol levels and higher serum HDL-cholesterol levels, respectively, compared with those harbouring the other LDLR pathogenic variants. The proportion of LDLR pathogenic variants was higher in patients with a younger age of coronary artery disease (CAD) onset and significantly decreased as the age of CAD onset increased. CONCLUSIONS: This study annotated the clinical significance and characteristics of LDLR and PCSK9 pathogenic variants in Japanese HeFH patients.

[7] *Chen C, Wang Y, Cao Y et al.* **Inhibitory effects and mechanism of probucol on elastase-induced abdominal aortic aneurysm in mice**. Br J Pharmacol 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31478560

ABSTRACT
BACKGROUND AND PURPOSE: Abdominal aortic aneurysm (AAA) is a degenerative disease with irreversible and progressive dilation of the artery. But there are few options for efficacious treatment except for traditional surgery. Probucol (PB) has been widely applied to treat hyperlipidemia and atherosclerosis in clinic, but whether it can protect against AAA remains unknown. In this study, the protective effects of PB against AAA and its related mechanisms were explored. EXPERIMENTAL APPROACH: Mouse AAA model was induced by incubating the abdominal aorta with elastase. PB at different doses was administrated to the mice by gavage beginning on the same day of AAA inducement and lasted for 14 days. In vitro experiments were constructed by stimulating rat vascular smooth muscle cells (VSMCs) with tumor necrosis factor (TNF)-alpha. Heme oxygenase (HO)-1 siRNA and HO-1 plasmid were used to regulate the expression or activity of HO-1 in the VSMCs and to clarify the effects of HO-1. KEY RESULTS: PB dose-dependently prevented the development of AAA, reflected by decrease of AAA incidence, diameters of aortic dilation, elastin degradation and inflammatory cells infiltration. PB could also protect VSMCs from oxidative injury and enhance elastin biosynthesis. But the anti-inflammatory effect of PB on VSMCs was weakened significantly when HO-1 was inhibited by siRNA. CONCLUSION AND IMPLICATIONS: PB exerted anti-AAA effects through inhibiting the degradation of elastin caused by inflammation and oxidation and facilitating the biosynthesis of elastin. HO-1 plays a crucial role in anti-inflammatory effect of PB on VSMCs.

[8] *Thermos G, Tosios KI*. **Gingival Ischemia and Petechiae in a Patient Medicated With PCSK9 Inhibitor for Hypercholesterolemia: An Adverse Drug Event?** Clinical advances in periodontics 2019; 9:20-23.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31490035

ABSTRACT

INTRODUCTION: Monoclonal antibodies against proprotein-convertase subtilisin/kexin type 9 (PCSK9) inhibitors are a newly-introduced therapeutic approach against hypercholesterolemia. Clinical trials have reported few adverse effects of PCSK9 inhibitors and there are no reports of oral adverse effects. We present the case of a patient that showed gingival discomfort on eating and toothbrushing, coupled with the presence of gingival ischemia and petechiae, 3 days after a subcutaneous abdominal injection of 75-mg alirocumab for hypercholesterolemia, and contemplate on their possible pathogenesis. CASE PRESENTATION: Alphan 81-year-old male presented with gingival discomfort during eating and toothbrushing, 3 days after receiving a subcutaneous abdominal injection of alirocumab. Intraoral examination revealed that the anterior free and attached gingiva of both jaws appeared pale and the surrounding mucosa showed confluent petechiae that were more evident on the anterior palatal gingiva. The patient was asked to brush his teeth with a soft toothbrush and use a mouthwash containing hydrogen peroxide three times daily. At the 8-day re-examination he was symptom-free, and the mucosa appeared totally normal. At the 5-month follow-up visit he reported having the same symptoms after each one of the 12 doses of alirocumab he received. CONCLUSIONS: Adverse dugs effects associated with subcutaneous injection of alirocumab may manifest in the gingiva. Therefore, oral and periodontal examination should be included in the regular follow-up of patients medicated with this drug.

[9] *Panahi Y, Ghahrodi MS, Jamshir M et al.* **PCSK9 and atherosclerosis burden in the coronary arteries of patients undergoing coronary angiography**. Clinical biochemistry 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31493378

ABSTRACT

AIMS: To investigate the association between plasma proprotein convertase subtilisin/kexin type 9 (PCSK9) concentrations, current acute coronary syndrome (ACS), coronary artery disease (CAD) presence, severity and extension and the burden of coronary calcifications in patients with suspected CAD. METHODS AND RESULTS: One hundred and one patients, with or without current ACS, were recruited for this cross-sectional study. CAD presence was defined based on either the presence or absence of at least one significant (>/=50%) CAD lesion (SCAD). CAD severity was classified according to the absence of coronary lesions, the presence of non-significant (<50%) CAD (MCAD) or SCAD in at least one major coronary artery. Patients with one, two or three significantly diseased major coronary arteries were defined as 1-SCAD, 2-SCAD and 3-SCAD, respectively. The cumulative length of SCAD lesions and the amount of calcifications in coronary arteries were estimated. Plasma PCSK9 concentrations were higher in patients with SCAD as compared to those without (p=.012). A significant increase in plasma PCSK9 concentrations was observed with greater CAD severity (p=.042). Higher plasma PCSK9 concentrations were found in 3-SCAD patients as compared to either 2-SCAD or 1-SCAD (p<.001). PCSK9 increased with the cumulative length of SCAD lesions and the burden of

calcifications (p<.05 for both comparisons). Multivariable adjustment abolished the association between PCSK9 and either CAD presence or severity, but not the association between PCSK9 and the number of significantly diseased vessels, SCAD lesion length and the burden of coronary calcifications. ACS was associated with a borderline significant increase of plasma PCSK9 concentrations among patients not taking statins (p=.05). CONCLUSION: Circulating PCSK9 concentrations discriminate patients with greater coronary atherosclerotic lesion extension and calcification, and are increased in patients with current ACS.

[10] *Truong TM, Lipschultz E, Danahey K et al.* **Assessment of patient knowledge and perceptions of pharmacogenomics before and after using a mock results patient web portal**. Clinical and translational science 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31490020
ABSTRACT
Our objective was to build a mock pharmacogenomic (PGx) patient portal and assess its ability to disseminate test results and information to patients. The YourPGx Portal delivered four sample PGx results (omeprazole, simvastatin, clopidogrel, and codeine). We hosted two study groups to assess patient knowledge and perceptions of PGx before and after accessing the portal. Ten PGx-tested and 10 traditional care (TC) participants were included (average 61 years, 60% women, 50% African-American, and 55% had a bachelor's/advanced degree). Participants scored significantly higher on the post-test compared to the pre-test, with no significant differences between baseline scores or score change between the groups. Patient perceptions also improved after accessing the portal - more patients wanted their providers to have access to test results, and more patients would encourage family/friends to get PGx testing. Patients would share their test results with their healthcare providers, spouse/partner, and family; none would share results with their friends or social media. Almost all patients (95%) said the portal was easy to use and 65% said it was easy to understand. In this pilot study, patients' knowledge and perceptions of PGx improved after accessing the YourPGx Portal.

[11] *Kigka VI, Sakellarios A, Kyriakidis S et al.* **A three-dimensional quantification of calcified and non-calcified plaques in coronary arteries based on computed tomography coronary angiography images: Comparison with expert's annotations and virtual histology intravascular ultrasound**. Computers in biology and medicine 2019; 113:103409.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31480007
ABSTRACT
The detection, quantification and characterization of coronary atherosclerotic plaques has a major effect on the diagnosis and treatment of coronary artery disease (CAD). Different studies have reported and evaluated the noninvasive ability of Computed Tomography Coronary Angiography (CTCA) to identify coronary plaque features. The identification of calcified plaques (CP) and non-calcified plaques (NCP) using CTCA has been extensively studied in cardiovascular research. However, NCP detection remains a challenging problem in CTCA imaging, due to the similar intensity values of NCP compared to the perivascular tissue, which surrounds the vasculature. In this work, we present a novel methodology for the identification of the plaque burden of the coronary artery and the volumetric quantification of CP and NCP utilizing CTCA

images and we compare the findings with virtual histology intravascular ultrasound (VH-IVUS) and manual expert's annotations. Bland-Altman analyses were employed to assess the agreement between the presented methodology and VH-IVUS. The assessment of the plaque volume, the lesion length and the plaque area in 18 coronary lesions indicated excellent correlation with VH-IVUS. More specifically, for the CP lesions the correlation of plaque volume, lesion length and plaque area was 0.93, 0.84 and 0.85, respectively, whereas the correlation of plaque volume, lesion length and plaque area for the NCP lesions was 0.92, 0.95 and 0.81, respectively. In addition to this, the segmentation of the lumen, CP and NCP in 1350 CTCA slices indicated that the mean value of DICE coefficient is 0.72, 0.7 and 0.62, whereas the mean HD value is 1.95, 1.74 and 1.95, for the lumen, CP and NCP, respectively.

[12] *Khan SU, Khan MU, Valavoor S et al.* **Association of lowering apolipoprotein B with cardiovascular outcomes across various lipid-lowering therapies: Systematic review and meta-analysis of trials**. European journal of preventive cardiology 2019:2047487319871733.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31475865
ABSTRACT
AIMS: The effect of therapeutic lowering of apolipoprotein B (apoB) on mortality and major adverse cardiovascular events is uncertain. It is also unclear whether these potential effects vary by different lipid-lowering strategies. METHODS: A total of 29 randomized controlled trials were selected using PubMed, Cochrane Library and EMBASE through 2018. We selected trials of therapies which ultimately clear apolipoprotein B particles by upregulating low-density lipoprotein receptor (LDL-R) expression (statins, ezetimibe, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, bile acid sequestrants) or therapies which reduce apolipoprotein B independent of LDL-R (cholesteryl ester transfer protein inhibitor, fibrates, niacin, omega-3 fatty acids) with sample size of >/=1000 patients and follow-up of >/=1 year. The meta-regression and meta-analyses were constructed using a random effects model. RESULTS: In 332,912 patients, meta-regression analyses showed relative risks of 0.95 for all-cause mortality (95% confidence interval 0.92-0.99) and 0.93 (0.88-0.98) for cardiovascular mortality for every 10 mg/dL decrease in apolipoprotein B by all interventions combined. Reduction in all-cause mortality was limited to statins (0.92 (0.86-0.98)). For MACE, the relative risk per 10 mg/dL reduction in apolipoprotein B was 0.93 (0.90-0.97) for all therapies combined, with both statin (0.88 (0.83-0.93)) and non-statin therapies (0.96 (0.94-0.99)). which clear apolipoprotein B by upregulating LDL-R showing significant reductions; whereas interventions which lower apolipoprotein B independent of LDL-R did not demonstrate this effect (1.02 (0.81-1.30)). CONCLUSION: While both statin and established non-statin therapies (PCSK9 inhibitor and ezetimibe) reduced cardiovascular risk per decrease in apolipoprotein B, interventions which reduce apolipoprotein B independently of LDL-R were not associated with cardiovascular benefit.

[13] *Zeng HT, Zhao M, Zhang ZX et al.* **Atorvastatin improves the cardiac function of rats after acute myocardial infarction through ERK1/2 pathway**. European review for medical and pharmacological sciences 2019; 23:7120-7127.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31486514
ABSTRACT

OBJECTIVE: To study the regulatory effect of atorvastatin (ATV) on the extracellular signal-regulated kinase (ERK) 1/2 pathway and explore its effect on acute myocardial infarction (AMI) rats. MATERIALS AND METHODS: The rat model of AMI was established, and the model rats were randomly divided into AMI group and ATV-AMI group, and Sham group was also set up. At 4 weeks after successful modeling, the cardiac function indexes of Sprague-Dawley (SD) rats were detected via magnetic resonance imaging (MRI) and echocardiography (ECG). After the rats were executed, the left ventricular weight index (LVWI) was measured, and the myocardial damage was detected via hematoxylin-eosin (HE) staining and terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL) staining. Moreover, the messenger ribonucleic acid (mRNA) expressions of collagen I and collagen III in myocardial tissues were detected via Real Time-Polymerase Chain Reaction (PCR), and the expressions of ERK1/2 pathway-related proteins in myocardial tissues were detected via Western blotting. RESULTS: After administration of ATV for AMI, the fractional shortening (FS%) and ejection fraction (EF%) were significantly restored. Compared with that in ATV-AMI group, LVWI was significantly increased in AMI group ($p<0.05$), indicating that ATV could improve the cardiac function after AMI. The results of HE staining and TUNEL staining showed that ATV-AMI group had slighter myocardial damage and significantly lower apoptosis rate than AMI group, indicating that ATV could reverse AMI through the ERK1/2 pathway. Besides, the mRNA expressions of collagen I and collagen III were higher in AMI group and ATV-AMI group than those in Sham group ($p<0.05$), while they were significantly lower in ATV-AMI group than those in AMI group ($p<0.05$). The expressions of ERK1/2 pathway-related proteins were also higher in AMI group and ATV-AMI group than those in Sham group ($p<0.05$). CONCLUSIONS: ATV can significantly improve the cardiac function of SD rats after AMI, whose mechanism is related to the expression of the ERK1/2 pathway.

[14] *Son KB*. **Generic atorvastatin and rosuvastatin in the South Korean market: time of introduction in relation to manufacturer characteristics**. Expert review of pharmacoeconomics & outcomes research 2019:1-8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31483158
ABSTRACT
Background: The competition for and market dynamics of generic medicines can be understood by analyzing manufacturers' behavior. In this study, we analyzed the various types of generic atorvastatin and rosuvastatin that were introduced onto the South Korean market from 2002 to 2018 and their corresponding manufacturers. Methods: Based on publicly available data, we selected drugs containing atorvastatin and rosuvastatin as active ingredients for the analysis. We calculated the time between the date of marketing approval for the first generic and that of the remaining generics. Then, we categorized manufacturers that marketed generics into first movers and latecomers. Results: We confirmed that many manufacturers have marketed generic drugs in South Korea and that manufacturers can be categorized as first movers and latecomers. Interestingly, latecomers account for a large portion of the manufacturers of generics, and they have entered the market steadily, even after the market matured with a number of manufacturers. Additionally, the characteristics of the manufacturers were closely related to manufacturers' behaviors in the market. Conclusions: The order-of-entry effect,

which is commonly observed in other markets, is marginal in the South Korean market, and this phenomenon is mainly explained by the rare price competition among generic manufacturers.

[15] *Juraschek SP, Simpson LM, Davis BR et al.* **Effects of Antihypertensive Class on Falls, Syncope, and Orthostatic Hypotension in Older Adults: The ALLHAT Trial**. Hypertension 2019; 74:1033-1040.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31476905
ABSTRACT
Hypertension treatment has been implicated in falls, syncope, and orthostatic hypotension (OH), common events among older adults. Whether the choice of antihypertensive agent influences the risk of falls, syncope, and OH in older adults is unknown. ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) was a randomized clinical trial that compared the effects of hypertension first-step therapy on fatal coronary heart disease or nonfatal myocardial infarction (1994-2002). In a subpopulation of ALLHAT participants, age 65 years and older, we determined the relative risk of falls, syncope, OH, or a composite based on Centers for Medicare and Medicaid Services and Veterans Affairs claims, using Cox regression. We also determined the adjusted association of self-reported atenolol use (ascertained at the 1-month visit for indications other than hypertension) on outcomes in Cox models adjusted for age, sex, and race. Among 23 964 participants (mean age 69.8+/-6.8 years, 45% women, 31% non-Hispanic black) followed for a mean of 4.9 years, we identified 267 falls, 755 syncopes, 249 OH, and 1157 composite claims. There were no significant differences in the cumulative incidences of events across randomized drug assignments. However, amlodipine increased risk of falls during the first year of follow-up compared with chlorthalidone (hazard ratio [95% CI]: 2.24 [1.06-4.74]; P=0.03) or lisinopril (hazard ratio [95% CI]: 2.61 [1.03-6.72]; P=0.04). Atenolol use (N=928) was not associated with any of the 3 individual or composite claims. In older adults, the choice of antihypertensive agent had no effect on risk of fall, syncope, or OH long-term. However, amlodipine increased risk of falls within 1 year of initiation. These short-term findings require confirmation. Clinical Trial Registration- URL: http://www.clinicaltrials.gov. Unique identifier: NCT00000542.

[16] *Li Z, Zhao T, Tan X et al.* **Polymorphisms in PCSK9, LDLR, BCMO1, SLC12A3, and KCNJ1 are Associated with Serum Lipid Profile in Chinese Han Population**. International journal of environmental research and public health 2019; 16.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31480784
ABSTRACT
Unfavorable serum lipid levels are the most important risk factors for coronary artery disease (CAD), cerebral infarction, and other cardiovascular and cerebrovascular diseases. This study included 2323 Han Chinese in southern China. We collected medical reports, lifestyle details, and blood samples of individuals and used the polymerase chain reaction-ligase detection reaction method to genotype single-nucleotide polymorphisms (SNPs). Two SNPs showed a strong evidence of association with total cholesterol (TC): rs1003723 and rs6413504 in the low-density lipoproteins receptor (LDLR). Two SNPs in LDLR showed a strong evidence of association with low-density lipoprotein cholesterol (LDL-C), rs1003723 and rs6413504. Two SNPs showed a strong evidence of association with triglycerides (TG), namely, rs662145 in pro-protein

convertase subtilisin-kexin type 9 (PCSK9) and rs11643718 in the solute carrier family 12 member 3 (SLC12A3). For the TC, LDL-C, and TG levels, these SNPs generated strong combined effects on these lipid levels. For each additional dangerous gene, TC increased by 0.085 mmol/L (p = 7.00 x 10(-6)), and LDL-C increased by 0.075 mmol/L (p = 9.00 x 10(-6)). The TG increased by 0.096 mmol/L (p = 2.90 x 10(-5)). Compared with those bearing no risk alleles, the risk of hypertriglyceridemia, hypercholesterolemia, and dyslipidemia increased in those with two or more risk alleles and one risk gene. Polymorphisms of PCSK9, LDLR, and SLC12A3 were associated with the plasma lipid levels in people in southern China. These results provide a theoretical basis for gene screening and the prevention of dyslipidemia.

[17] *Koskinas KC, Windecker S, Pedrazzini G et al.* **Evolocumab for Early Reduction of LDL-Cholesterol Levels in Patients with Acute Coronary Syndromes (EVOPACS)**. Journal of the American College of Cardiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31479722
ABSTRACT
BACKGROUND: While guidelines recommend in-hospital initiation of high-intensity statin therapy in patients with acute coronary syndromes (ACS), low-density lipoprotein cholesterol (LDL-C) target levels are frequently not attained. Evolocumab, a rapidly acting, potent LDL-C-lowering drug, has not been studied in the acute phase of ACS. OBJECTIVES: To assess the feasibility, safety, and LDL-C lowering efficacy of evolocumab initiated during the in-hospital phase of ACS. METHODS: We conducted an investigator-initiated, randomized, double-blind, placebo-controlled trial involving 308 patients hospitalized for ACS with elevated LDL-C levels (>/=1.8 mmol/L on high-intensity statin for at least 4 weeks; >/=2.3 mmol/L on low- or moderate-intensity statin; or >/=3.2 mmol/L on no stable dose of statin). Patients were randomly assigned 1:1 to receive subcutaneous evolocumab 420mg or matching placebo, administered in-hospital and after 4 weeks, on top of atorvastatin 40mg. The primary endpoint was percentage change in calculated LDL-C from baseline to 8 weeks. RESULTS: Most patients (78.2%) had not been on previous statin treatment. Mean LDL-C levels decreased from 3.61 mmol/L to 0.79 mmol/L at week 8 in the evolocumab group, and from 3.42 mmol/L to 2.06 mmol/L in the placebo group; the difference in mean percentage change from baseline was -40.7% (95% CI: -45.2 to -36.2; p<0.001). LDL-C levels <1.8 mmol/L were achieved at week 8 by 95.7% of patients in the evolocumab group vs. 37.6% in the placebo group. Adverse events and centrally adjudicated cardiovascular events were similar in both groups. CONCLUSIONS: In this first randomized trial assessing a PCSK9 antibody in the very high-risk setting of ACS, evolocumab added to high-intensity statin therapy was well tolerated and resulted in substantial reduction in LDL-C levels, rendering >95% of patients within currently recommended target levels.

[18] *Komatsu T, Uehara Y*. **What Kind of Probucol Affects Normalizing Male Birth?** Journal of atherosclerosis and thrombosis 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31484853
ABSTRACT

[19] *Ruszkowski P, Masajtis-Zagajewska A, Nowicki M*. **Effects of combined statin and ACE inhibitor therapy on endothelial function and blood pressure in essential hypertension - a randomised double-blind, placebo controlled crossover study**. Journal of the renin-angiotensin-aldosterone system : JRAAS 2019; 20:1470320319868890.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31486700

ABSTRACT

BACKGROUND: The aim of this study was to compare the influence of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors on endothelial function and blood pressure in patients with essential hypertension on long-term angiotensin-converting enzyme inhibitor therapy. METHOD: The study was designed as a prospective, double-blind, randomised, placebo controlled, crossover clinical trial. Twenty patients with essential hypertension were treated with an angiotensin-converting enzyme inhibitor; the control group included 10 healthy subjects. Hypertensive patients received in random order 80 mg of fluvastatin daily or placebo for 6 weeks. The following parameters were assessed at baseline and after each treatment period: serum lipids, flow-mediated vasodilation, activity of von Willebrand factor, concentration of vascular endothelial growth factor, C-reactive protein and 24-hour blood pressure profile. RESULTS: Hypertensive patients did not differ from healthy subjects with respect to age, body mass and biochemical parameters, with the exception of C-reactive protein, which was higher in hypertensive patients (P=0.02). After statin therapy, low-density lipoprotein cholesterol (P<0.0001), C-reactive protein (P=0.03), von Willebrand factor (P=0.03) and vascular endothelial growth factor (P<0.01) decreased and flow-mediated vasodilation improved (P<0.001). Statins had no significant effect on blood pressure. CONCLUSIONS: Statins added to angiotensin-converting enzyme inhibitors may improve endothelial function and ameliorate inflammation independently of blood pressure.

[20] *Lin JK, Moran AE, Bibbins-Domingo K et al.* **Cost-effectiveness of a fixed-dose combination pill for secondary prevention of cardiovascular disease in China, India, Mexico, Nigeria, and South Africa: a modelling study**. The Lancet. Global health 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31477544

ABSTRACT

BACKGROUND: Fewer than 25% of patients with atherosclerotic cardiovascular disease in countries of low and middle income (LMICs) use guideline-directed drugs for secondary prevention. A fixed-dose combination polypill might improve cardiovascular outcomes by increasing prescription rates and adherence, but the cost-effectiveness of this approach is uncertain. METHODS: We developed microsimulation models to assess the cost-effectiveness of a polypill containing aspirin, lisinopril, atenolol, and simvastatin for secondary prevention of atherosclerotic cardiovascular disease compared with current care in China, India, Mexico, Nigeria, and South Africa. We modelled baseline use of secondary prevention drugs on the Prospective Urban Rural Epidemiological study. In the intervention arm, we assumed that patients currently prescribed any prevention drug for atherosclerotic cardiovascular disease would receive the polypill instead, which would improve adherence by 32% (from a meta-analysis of two randomised trials in LMICs). We assessed the cost-effectiveness of the polypill at prices in the public sector and on the retail market. Key outcomes were major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal

stroke) over a 5-year period and the incremental cost-effectiveness ratio (ICER) from the perspective of the health-care sector and a lifetime analytical horizon. We assumed a cost-effectiveness threshold equal to each country's per capita gross domestic product (GDP) per disability-adjusted life-year (DALY) averted. In sensitivity analyses, we examined the population health effect achievable by increasing the uptake of the polypill in the eligible population. FINDINGS: Among adults aged 30-84 years with established atherosclerotic cardiovascular disease, adoption of the polypill for secondary prevention compared with current care was projected to avert 40-54 major adverse cardiovascular events for every 1000 patients treated for 5 years and produce between three and ten additional serious adverse events. Assuming public-sector pharmaceutical prices, the ICER of the polypill compared with current care over a lifetime analytical horizon was Int$168 (95% UI 55 to 337) per DALY averted in China, $154 (57 to 289) in India, $88 (15 to 193) in Mexico, $364 (147 to 692) in Nigeria, and $64 (cost-saving to 203) in South Africa, amounting to 0.4-6.2% of the per capita GDP in these countries. The ICER of the polypill compared with current care increased to 3.3-14.6% of the per capita GDP at retail market pharmaceutical prices. Use of the polypill at current rates of prescription of secondary prevention drugs would produce modest health benefits, reducing DALYs from atherosclerotic cardiovascular disease among patients with established disease by 3.1-10.1% over 10 years. Increasing use to 50% or 75% of the eligible population would produce substantially larger health gains (up to 24.3% atherosclerotic cardiovascular disease DALYs averted). INTERPRETATION: The polypill is projected to be cost-effective compared with current care for secondary prevention of atherosclerotic cardiovascular disease in China, India, Mexico, Nigeria, and South Africa, particularly if it is made available at public-sector pricing. However, achieving meaningful improvements in cardiovascular health will require simultaneous investments in health infrastructure to increase the uptake of the polypill among patients with established atherosclerotic cardiovascular disease. FUNDING: Richard A and Susan F Smith Center for Outcomes Research in Cardiology, Hellman Family Foundation, Department of Veterans Affairs, and University of California at San Francisco.

[21] *Nabi R, Alvi SS, Shah A et al.* **Modulatory role of HMG-CoA reductase inhibitors and ezetimibe on LDL-AGEs-induced ROS generation and RAGE-associated signalling in HEK-293 Cells**. Life sciences 2019; 235:116823.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31476307
ABSTRACT
AIMS: Advanced glycation end products (AGEs) trigger intracellular reactive oxygen species (ROS) generation, activation of receptor for AGEs (RAGE) expression/functionality and RAGE-associated signalling pathways which influence the diabetic-cum-atherosclerotic complications, whereas, the atherosclerosis progression is greatly influenced by hepatic beta-Hydroxy-beta-methyl-glutaryl-Co-A reductase (HMG-R) activity. The present report was premeditated to uncover the regulatory role of HMG-R inhibitors and ezetimibe (EZ) in attenuating the LDL-AGEs-induced pathogenicity via targeting cellular-ROS and RAGE-associated signalling in HEK-293 cells. MAIN METHODS: The MTT assay was used to assess either the cytotoxic or cytoprotective impact of each HMG-R inhibitors, EZ, and LDL-AGEs, whereas, quantification of ROS was performed by DCFDA method. The qRT-PCR was used to detect the mRNA level of RAGE, neuropilin-1 (NRP-1) and other RAGE-associated genes like MMP-2, NF-kappaB, and

TGFbeta-1. KEY FINDINGS: The HMG-R inhibitors do not exert any cytotoxicity in HEK-293 cells, whereas, and LDL-AGEs negatively affected the cell viability of HEK-293 cells. However, viability of LDL-AGEs-treated HEK-293was markedly retained after simultaneous treatment with our test inhibitors. Further, DCFDA staining showed that LDL-AGEs-induced ROS was also suppressed upon treatment with our test inhibitors in HEK-293 cells. qRT-PCR analysis reflected that these inhibitors suppress the RAGE, NF-kappaB, TGFbeta-1, and MMP-2 expression, whereas, the NRP-1 was up-regulated by these compounds in LDL-AGEs-exposed HEK-293 cells. SIGNIFICANCE: The above pharmacological effects signify that HMG-R inhibitors and EZ (alone or in combination) may implied in the treatment of AGEs-induced oxidative stress and tissue damage in diabetic complications via targeting intracellular-ROS, NRP-1 functionality and RAGE-associated genes i.e. NF-kappaB, TGFbeta-1, and MMP-2.

[22] *Lian Y, Xie L, Liu Y, Tang F*. **Metabolic-related markers and inflammatory factors as predictors of dyslipidemia among urban Han Chinese adults**. Lipids in health and disease 2019; 18:167.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31472689
ABSTRACT
BACKGROUND: Metabolic-related markers and inflammatory factors have been proved to be associated with increased risk of dyslipidemia. Elucidating the mechanisms underlying these associations might provide an important perspective for the prevention of dyslipidemia. In the present study, we aimed to explore the effect of metabolic-related markers on dyslipidemia, and to assess what extent inflammation mediating these associations. METHODS: A total of 25,130 participants without dyslipidemia at baseline were included in the present study during 2010-2015. A partial least squares path model was used to explore possible pathways from metabolic-related markers to dyslipidemia, and the mediation role of inflammation. RESULTS: Lipid metabolism factor, blood pressure factor, obesity condition factor, glucose metabolism factor, renal function factor and lifestyle factor had diverse impact on development of dyslipidemia, directly and (or) indirectly. Partial least squares path analysis revealed that the determination coefficient of the model (R(2)) was 0.52. Lipid metabolism factor, obesity condition factor, and glucose metabolism factor had both direct and indirect effect on dyslipidemia through inflammatory factor. Lipid metabolism factor was the most important risk factor (beta = 0.68) in the prediction of dyslipidemia, followed by obesity condition factor (beta = 0.06) and glucose metabolism factor (beta = 0.03). CONCLUSIONS: Metabolic-related markers are strong risk factors for dyslipidemia. Inflammatory factors have significant mediating effect on these relationships. These findings suggested that comprehensive intervention strategies on metabolic biomarkers and inflammatory factors should be taken into consideration in prevention and treatment of dyslipidemia.

[23] *Bijl D*. **[How transparent is the new Dutch guideline on cardiovascular risk management?]**. Ned Tijdschr Geneeskd 2019; 163.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31483586
ABSTRACT
The new Dutch guideline on cardiovascular risk management has lowered the target value for LDL cholesterol from 2.5 to 1.8 mmol/L. The authors claim transparency, yet there is no hard

scientific evidence that supports this new target value. There is only a theoretical model developed by theCholesterol Treatment Trialists' (CTT) Collaboration Group. This group has the raw data of the cholesterol trials and they have signed confidentiality agreements with manufacturers stating that they will not share this data with others. This group also produced the Cochrane review on primary cardiovascular prevention with statins. If the real effect of cholesterol-lowering drugs is not disclosed to the population in a transparent manner, this will be done through independent channels with the message 'leave those PCSK9 inhibitors alone until there is hard scientific evidence for their efficacy.' And if patients suffer greatly from, for example,muscle pain, diabetes or amnesia due to taking statins, in accordance with the guideline they will decide for themselves whether or not to continue taking it.

[24] *Senoner T, Dichtl W*. **Oxidative Stress in Cardiovascular Diseases: Still a Therapeutic Target?** Nutrients 2019; 11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31487802
ABSTRACT
Cardiovascular diseases (CVD) are complex entities with heterogenous pathophysiologic mechanisms and increased oxidative stress has been viewed as one of the potential common etiologies. A fine balance between the presence of reactive oxygen species (ROS) and antioxidants is essential for the proper normal functioning of the cell. A basal concentration of ROS is indispensable for the manifestation of cellular functions, whereas excessive levels of ROS cause damage to cellular macromolecules such as DNA, lipids and proteins, eventually leading to necrosis and apoptotic cell death. CVD is the main cause of death worldwide with several conditions being affected by oxidative stress. Increased ROS lead to decreased nitric oxide availability and vasoconstriction, promoting arterial hypertension. ROS also negatively influence myocardial calcium handling, causing arrhythmia, and augment cardiac remodeling by inducing hypertrophic signaling and apoptosis. Finally, ROS have also been shown to promote atherosclerotic plaque formation. This review aims at giving an introduction into oxidative stress in CVD, with special focus on endothelial dysfunction, and then examining in detail the role of oxidative stress in the most prevalent of these diseases. Finally, potential nutraceuticals and diets that might be beneficial in diminishing the burden of oxidative stress in CVD are presented.

[25] *Flannagan KS, Sjaarda LA, Hill MJ et al.* **Pilot randomized trial of short-term changes in inflammation and lipid levels during and after aspirin and pravastatin therapy**. Reproductive health 2019; 16:132.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31477152
ABSTRACT
BACKGROUND: Inflammation and elevated blood lipids are associated with infertility. Aspirin and statin therapy may improve infertility treatment outcomes among overweight and obese women with systemic inflammation, but little is known about the short-term effects of statins in this population. We conducted a pilot study of aspirin, pravastatin, or combined treatment among a group of overweight and obese, reproductive-aged women. Our goal was to characterize short-term changes in inflammatory and lipid biomarkers during and after treatment. METHODS: In this open-label trial, women aged 18-40 years with a body mass index

>/=25 kg/m(2) were randomized to receive either 162 mg aspirin, 40 mg pravastatin, or both. The study medication was taken daily for 2 weeks, and participants were then followed for a two-week washout period. Participants provided blood samples at baseline, after the intervention period, and after the washout period. The outcomes were changes in biomarkers of inflammation and lipids measured in blood components at each timepoint. RESULTS: Nine, 8, and 8 women were randomized to the aspirin, pravastatin, and combined arms, respectively. Analyses were conducted among 8, 7, and 7 women in the aspirin, pravastatin, and combined arms for whom biomarker data was available at baseline. High-sensitivity C-reactive protein (hsCRP) levels were lower after treatment in all arms and continued to decrease after washout in the pravastatin and combined arms. Results were consistent between the whole sample and women with baseline hsCRP between 2 and 10 mg/L. Low-density lipoprotein (LDL) cholesterol was lower after treatment in the pravastatin and combined arms and rose slightly after washout. CONCLUSIONS: Our results provide preliminary evidence that short-term aspirin and pravastatin therapy reduces hsCRP and LDL cholesterol among overweight and obese women of reproductive age, including those with low-grade inflammation. Because of these short-term effects, these drugs may improve infertility treatment outcomes in this population, which we will assess in a future randomized trial.

[26] *Groba-Marco MDV, Del Castillo-Garcia S, Barge-Caballero G et al.* **Treatment of hypercholesterolemia with PCSK9 inhibitors in heart transplant recipients. First experience in Spain**. Revista espanola de cardiologia (English ed.) 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31474577
ABSTRACT

[27] *Birck MG, Goulart AC, Lotufo PA, Bensenor IM*. **Secondary prevention of coronary heart disease: a cross-sectional analysis on the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil)**. Sao Paulo medical journal = Revista paulista de medicina 2019; 137:223-233.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31483010
ABSTRACT
BACKGROUND: Coronary heart disease (CHD) remains a major cause of mortality worldwide and in Brazil. Use of standard medications after CHD has been proven to avoid new events and reduce early mortality. OBJECTIVES: This study aimed to analyze secondary prevention of CHD and its association with the baseline characteristics of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). DESIGN AND SETTING: Cross-sectional analysis on ELSA-Brasil data. METHODS: Secondary prevention of CHD recommended in standard guidelines (antiplatelet plus beta-blocker plus lipid-lowering drug, with or without angiotensin-converting enzyme inhibitors, ACEI, or angiotensin receptor blockers, ARB) was evaluated in relation to sociodemographic data and the time since the coronary event. The chi-square test, one-way analysis of variance (ANOVA) and Mann-Whitney test were performed, as necessary. RESULTS: Among 15,094 participants, 2.7% reported a previous diagnosis of CHD. Use of recommended drugs for secondary prevention was reported by almost 35% of the participants. Medication use for secondary prevention was generally more frequent among high-income participants than among low-income participants. Use of ARB and ACEI was different between participants who had private health insurance and those who only used the public healthcare system. Men were

more likely to use medication than women. The frequency with which participants used the recommended drugs was similar in all time periods after CHD, but use of only one drug increased progressively across time periods. CONCLUSION: The use of medication for secondary prevention of CHD was lower than what is recommended in standardized guidelines, especially among women and lower-income participants.

[28] *Koh KH, Goh CC, Goh SCP et al.* **Blood pressure goal attainment in multi-ethnic Asian patients with hypertension and dyslipidaemia in primary care**. Singapore medical journal 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31489431
ABSTRACT
INTRODUCTION: Hypertension and dyslipidaemia are major risk factors for cardiovascular diseases, and achieving treatment goals mitigates such risks. This study determined demographic and medication-related factors associated with blood pressure (BP) goal attainment in patients with concomitant hypertension and dyslipidaemia. METHODS: This paper consisted of a sub-analysis of the Lipid HEALTH study, a questionnaire survey focusing on adult Asian patients with both dyslipidaemia and hypertension. Interviewer-administered questionnaire was used to obtain information on demographic and clinical information. Laboratory and prescription data was retrieved from electronic health records. BP goals were defined by international guidelines. Data was audited and analysed, followed by logistic regression analysis to identify factors determining BP goal attainment. RESULTS: The complete data of 851 included patients were analysed; 49.7% of them attained their BP goals. 37% were on monotherapy, 57.6% on two or more BP-lowering medications, and 5.5% had no pharmacologic treatment. Among those on pharmacotherapy, 51.2% failed to achieve BP goals. Calcium channel blockers were the most frequently prescribed medications. Attainment of BP goals was significantly associated who had no type 2 diabetes mellitus (DM) (OR 2.27; 95% CI 1.61-3.13); attained low-density lipoprotein cholesterol (LDL-C) goal (OR 2.02; 95% CI 1.45-.81); were solely on dietary control (OR 2.19; 95% CI 1.09-4.39); and received monotherapy (OR 1.71; 95% CI 1.18-2.48). CONCLUSION: BP treatment goals were attained by half of the patients with dyslipidaemia and hypertension, and half of those on pharmacotherapy. Type 2 DM and LDL-C control were significantly associated with BP goal attainment.

[29] *Schreiber K, Hunt BJ*. **Managing antiphospholipid syndrome in pregnancy**. Thrombosis research 2019; 181 Suppl 1:S41-s46.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31477227
ABSTRACT
Antiphospholipid syndrome (APS) is an autoimmune disease characterised by the presence of antiphospholipid antibodies (aPL). The antibodies currently included in the classification criteria include lupus anticoagulant (LA), anticardiolipin antibodies (aCL) and anti-^2-glycoprotein 1 antibodies (^2GPI). APS can present with a variety of clinical phenotypes, including thrombosis in the veins, arteries and microvasculature and obstetrical complications. Pregnancy complications in obstetric APS (OAPS) include unexplained recurrent early pregnancy loss, fetal death, or premature birth due to severe preeclampsia, eclampsia, intrauterine growth restriction or other consequences of placental insufficiency. Careful, well monitored obstetric

care with the use of aspirin and heparin has likely improved the pregnancy outcome in obstetric APS and currently approximately 70-80% of pregnant women with APS have a successful pregnancy outcome. However, the current standard of care does not prevent all pregnancy complications as the current treatment fails in 20-30% of APS pregnancies. Other treatments options are currently being explored and retrospective studies suggest that trials with hydroxychloroquine and possibly pravastatin are warranted in pregnant women with aPL. In this review will focus on the current treatment of OAPS.

[30] *Thonusin C, Apaijai N, Jaiwongkam T et al.* **The comparative effects of high dose atorvastatin and proprotein convertase subtilisin/kexin type 9 inhibitor on the mitochondria of oxidative muscle fibers in obese-insulin resistant female rats**. Toxicology and applied pharmacology 2019; 382:114741.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31473249
ABSTRACT
The present study aimed to compare the effects of high dose atorvastatin and a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor on the mitochondrial function in oxidative muscle fibers in obese female rats. Female Wistar rats were fed with either a normal diet (ND: n=12) or a high-fat diet (HFD: n=36) for a total of 15weeks. At week 13, ND-fed rats received a vehicle, and HFD-fed rats were divided to three groups to receive either a vehicle, 40mg/kg/day of atorvastatin, or 4mg/kg/day of PCSK9 inhibitor (SBC-115076) for 3weeks. Soleus muscles were investigated to assess mitochondrial ROS, membrane potential, swelling, mitochondrial-related protein expression, and level of malondialdehyde (MDA). The results showed that HFD-fed rats with vehicle developed obese-insulin resistance and dyslipidemia. Both atorvastatin and PCSK9 inhibitor reduced obesity and dyslipidemia, as well as improved insulin sensitivity in HFD-fed rats. However, the efficacy of PCSK9 inhibitor to increase weight loss and reduce dyslipidemia in HFD-fed rats was greater than those of atorvastatin. An increase in MDA level, ratio of p-Drp1(ser616)/total Drp1 protein, CPT1 protein, mitochondrial ROS, and membrane depolarization in the soleus muscle were observed in HFD-fed rats with vehicle. PCSK9 inhibitor enabled the restoration of all these parameters to normal levels. However, atorvastatin facilitated restoration of some parameters, including MDA level, p-Drp1(ser616)/total Drp1 ratio, and CPT1 protein expression. These findings suggest that PCSK9 inhibitor is superior to atorvastatin in instigating weight loss, cholesterol reduction, and attenuation of mitochondrial oxidative stress in oxidative muscle fibers of obese female rats.

[31] *Irwin JC, Fenning AS, Vella RK*. **Geranylgeraniol prevents statin-induced skeletal muscle fatigue without causing adverse effects in cardiac or vascular smooth muscle performance**. Translational research : the journal of laboratory and clinical medicine 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31491372
ABSTRACT
The administration of geranylgeranyl pyrophosphate (GGPP) (or its precursor, geranylgeraniol [GGOH]) has been shown by several in vitro studies to be capable of abrogating statin-induced myotoxicity. Nonetheless, the potential of GGPP repletion to prevent statin-associated muscle symptoms (SAMS) in vivo is yet to be investigated. Therefore, this study aimed to evaluate the ability of GGOH to prevent SAMS in rodents. Female Wistar rats (12 weeks of age) were

randomised to 1 of 4 treatment groups: control, control with GGOH, simvastatin or simvastatin with GGOH. Ex vivo assessment of force production was conducted in skeletal muscles of varying fiber composition. Ex vivo left ventricular performance and blood vessel function was also assessed to determine if the administration of GGOH caused adverse changes in these parameters. Statin administration was associated with reduced force production in fast-twitch glycolytic muscle, but coadministration with GGOH completely abrogated this effect. Additionally, GGOH improved the performance of muscles not adversely affected by simvastatin (ie, those with a greater proportion of slow-twitch oxidative fibers), and increased force production in the control animals. Neither control nor statin-treated rodents given GGOH exhibited adverse changes in cardiac function. Vascular relaxation was also maintained following treatment with GGOH. The findings of this study demonstrate that GGOH can prevent statin-induced skeletal muscle fatigue in rodents without causing adverse changes in cardiovascular function. Further studies to elucidate the exact mechanisms underlying the effects observed in this investigation are warranted.

[32] *Jennings DL, Jackson R, Farr M*. **PCSK9 Inhibitor Use in Heart Transplant Recipients: A Case Series and Review of the Literature**. Transplantation 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31478991
ABSTRACT

[33] *Kayikcioglu M, Alan B, Payzin S, Can LH*. **[Lipid profile, familial hypercholesterolemia prevalence, and 2-year cardiovascular outcome assessment in acute coronary syndrome: Real-life data of a retrospective cohort]**. Turk Kardiyoloji Dernegi arsivi : Turk Kardiyoloji Derneginin yayin organidir 2019; 47:476-486.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31483296
ABSTRACT
OBJECTIVE: The aim of this retrospective study based on real-life data was to evaluate the lipid profile and demographic, clinical, and laboratory features of patients with acute coronary syndrome (ACS) at a tertiary center and to examine the mortality rate. METHODS: Information including endpoint data for at least 2 years following the index ACS event was retrieved from hospital records. Patients without sufficient follow-up data were called by phone. Modified Dutch Lipid Clinic Network criteria were used to identify the presence of familial hypercholesterolemia (FH). Factors affecting mortality in the 2-year follow-up period were evaluated using Cox regression analysis. RESULTS: A total of 985 ACS patients (215 females) between 21 and 93 years of age were included. The females were older and had a lower smoking rate than the males. In females, the history of obesity and hypertension, the diabetes rate, and the thyroid-stimulating hormone level were higher than those of the males. In 95.6% of the patients, lipid parameters were measured upon hospital admission. No significant difference in dyslipidemia frequency was observed between genders. The frequency of FH was 7.6%. The rate of lipid-lowering drug use was <20% at admission, >90% at discharge, and decreased to 50% in the follow-up period. The mortality rate was 3.8% in the in-hospital period and 8.1% during the 2 years of follow-up. CONCLUSION: The mortality rate in ACS patients was 3.8% in the in-hospital period and 8.1% in the 2-year follow-up period. The frequency of hypercholesterolemia was 89.5% and the rate of lipid-lowering drug use was insufficient.

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Secondary prevention after ACS was not adequately employed even at a tertiary center. The FH frequency was 7.6% and those with FH were observed to have ACS at a younger age than those without.