[1] *Cao YX, Li L, Zhang HW et al.* **Visit-to-visit variability of lipid and cardiovascular events in patients with familial hypercholesterolemia**. Annals of translational medicine 2021; 9:556.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33987254

ABSTRACT

BACKGROUND: Visit-to-visit variability in lipid has been suggested as a predictor of major adverse cardiovascular events (MACEs). However, no evidence exists on the prognostic value of lipid variability in patients with familial hypercholesterolemia (FH). This prospective cohort study aimed to investigate whether lipid variability affects future MACEs in patients with FH receiving standard lipid-lowering therapy. METHODS: A total of 254 patients with FH were consecutively enrolled and followed for MACEs. Variability in the triglyceride, total cholesterol, high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C) and lipoprotein (a) [Lp(a)] were evaluated from 3 months after discharge using the standard deviation (SD), coefficient of variation (CV) and variability independent of the mean (VIM). RESULTS: During a mean follow-up of 49 months, 22 (8.7%) events occurred. Visit-to-visit variability in Lp(a) was significantly higher in the MACE group compared to the non-MACE group. In the multivariate Cox analysis, only Lp(a)-related parameters were independent predictors for MACEs. The hazard ratios and 95% confidence intervals of each 1-SD increase of SD, CV, and VIM of Lp(a) were 1.42 (1.12-1.80), 1.50 (1.11-2.02) and 1.60 (1.16-2.22), respectively. Kaplan-Meier analysis revealed that patients with higher Lp(a) variability presented lower event-free survival. The results were consistent in various subgroups. CONCLUSIONS: Our study firstly suggested that Lp(a) variability was associated with MACEs in real-world patients with FH, which emphasized the importance of regular lipid monitoring in the patients with high risk.

[2] *Peyot ML, Roubtsova A, Lussier R et al.* **Substantial PCSK9 inactivation in β-cells does not modify glucose homeostasis or insulin secretion in mice**. Biochimica et biophysica acta. Molecular and cell biology of lipids 2021; 1866:158968.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33992809

ABSTRACT

Proprotein convertase subtilisin/kexin type 9 (PCSK9) plays an important role in cholesterol homeostasis by promoting the degradation of the LDL receptor (LDLR). PCSK9 loss-of-function mutations are associated with increased fasting plasma glucose levels and slightly elevated risk of type 2-diabetes. Considering the known detrimental effects of cholesterol accumulation in β-cell, and the widespread use of PCSK9 inhibitors to treat hypercholesterolemia, it is important to gain insight into the role of pancreatic PCSK9 in glucose homeostasis and β-cell function. We generated the first β-cell-specific KO of PCSK9 (βKO). PCSK9 mRNA and protein expression were reduced by 48% and 78% in βKO islets, respectively, indicating that β-cells constitute a major site of PCSK9 expression. In islets, loss of β-cell PCSK9 resulted in unchanged LDLR protein levels, but reduced LDLR mRNA, indicating that cholesterol internalization is enhanced and that β-cell PCSK9 promotes LDLR degradation. In contrast, whole body PCSK9 KO mice exhibited 2-fold higher LDLR protein levels in islets and a stable expression of cholesterogenic genes. Whole body KO and βKO mice presented normal glucose tolerance, insulin release in response to glucose load and insulin sensitivity. Ex vivo glucose-stimulated insulin secretion in presence or absence of fatty acids was similar in WT and KO islets. Like KO mice, individuals carrying loss-of-function PCSK9 variants may be protected from cholesterol-induced toxicity due to reduced circulating cholesterol levels. Using both whole body KO

or βKO models, our data demonstrate that PCSK9 deletion in mouse does not have any toxic effect on β-cell function and glucose homeostasis.

[3] *Ma Q, Liao X, Shao C et al.* **Normalization of γ-glutamyl transferase levels is associated with better metabolic control in individuals with nonalcoholic fatty liver disease**. BMC gastroenterology 2021; 21:215.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33971815
ABSTRACT
BACKGROUND: The normalization of liver biochemical parameters usually reflects the histological response to treatment for nonalcoholic fatty liver disease (NAFLD). Researchers have not clearly determined whether different liver enzymes exhibit various metabolic changes during the follow-up period in patients with NAFLD. METHODS: We performed a retrospective analysis of patients with NAFLD who were receiving therapy from January 2011 to December 2019. Metabolism indexes, including glucose levels, lipid profiles, uric acid levels and liver biochemical parameters, were measured. Magnetic resonance imaging-based proton density fat fraction (MRI-PDFF) and liver ultrasound were used to evaluate steatosis. All patients received recommendations for lifestyle modifications and guideline-recommended pharmacological treatments with indications for drug therapy for metabolic abnormalities. RESULTS: Overall, 1048 patients with NAFLD were included and received lifestyle modification recommendations and pharmaceutical interventions, including 637 (60.7%) patients with abnormal GGT levels and 767 (73.2%) patients with abnormal ALT levels. Patients with concurrent ALT and GGT abnormalities presented higher levels of metabolism indexes and higher liver fat content than those in patients with single or no abnormalities. After 12 months of follow-up, the cumulative normalization rate of GGT was considerably lower than that of ALT (38% vs. 62%, $P<0.001$). Greater weight loss resulted in higher cumulative normalization rates of GGT and ALT. Weight loss (OR = 1.21, 95% CI 1.11-1.32, $P<0.001$), ALT normalization (OR = 2.75, 95% CI 1.41-5.36, $P=0.01$) and lower TG and HOMA-IR values (OR = 2.03, 95% CI 1.11-3.71, $P=0.02$; OR = 2.04, 95% CI 1.07-3.89, $P=0.03$) were independent protective factors for GGT normalization. Elevated baseline GGT (OR = 0.99, 95% CI 0.98-0.99, $P=0.01$) was a risk factor. CONCLUSIONS: For NAFLD patients with concurrently increased ALT and GGT levels, a lower normalization rate of GGT was observed, rather than ALT. Good control of weight and insulin resistance was a reliable predictor of GGT normalization.

[4] *Ponna PK, Agrawal Y, Kassier A, Kalavakunta JK*. **Optical coherence tomography: high-resolution imaging modality useful in identifying the pathophysiology of coronary vasospasm in acute coronary syndrome**. BMJ case reports 2021; 14.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33972308
ABSTRACT

[5] *Nakajima K, Higuchi R, Mizusawa K, Nakamura T*. **Association between extremely high high-density lipoprotein-cholesterol and hypertensive retinopathy: results of a cross-sectional study from Kanagawa Investigation of Total Checkup Data from the National Database-6 (KITCHEN-6)**. BMJ open 2021; 11:e043677.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33980518
ABSTRACT

OBJECTIVES: Doubt has been cast on the atheroprotective effect of very high high-density lipoprotein cholesterol (HDL-C). Hypertensive retinopathy (HR) is caused by persistent systemic hypertension. Therefore, we aimed to investigate the association between extremely high HDL-C (EH-HDL) and HR. DESIGN: A cross-sectional study. PARTICIPANTS: A total of 4072 general Japanese population aged 40-74 years who underwent regular medical check-ups including fundus examinations. OUTCOME MEASURES: HR and clinical parameters including serum HDL-C were investigated. HR was determined by the Keith-Wagener classification and the Scheie classifications for Hypertension and Atherosclerosis (n=4054 available). Serum HDL-C was divided into five categories: 30-49, 50-69, 70-89, 90-109 and ≥110 mg/dL. RESULTS: Overall, 828 (20.3%) subjects had Keith-Wagener-HR, 578 (14.3%) had hypertension-HR, and 628 (15.5%) had atherosclerosis-HR. Blood pressure decreased as HDL-C level increased, whereas the prevalences of HRs showed U-shaped curves against HDL-C with minimum values for HDL-C 90-109 mg/dL. In logistic regression analyses, EH-HDL ≥110 mg/dL was significantly associated with Keith-Wagener-HR and atherosclerosis-HR, compared with HDL-C 90-109 mg/dL after adjustments for age, sex and systolic blood pressure (OR 3.01, 95% CI 1.45 to 6.27 and OR 2.23, 95% CI 1.03 to 4.86). The hypertension-HR was not significantly associated with EH-HDL regardless of adjustment for the confounding factors (p=0.05-0.08). Although serum HDL-C as a continuous variable was inversely associated with three HRs, which disappeared after adjustment for the confounding factors. CONCLUSION: EH-HDL may be associated with HR independently of blood pressure, suggesting that EH-HDL reflects a special atherosclerotic condition.

[6] *Puato M, Zambon A, Nardin C et al.* **Lipid Profile and Vascular Remodelling in Young Dyslipidemic Subjects Treated with Nutraceuticals Derived from Red Yeast Rice**.
Cardiovascular therapeutics 2021; 2021:5546800.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33976708

ABSTRACT

BACKGROUND AND AIMS: A relevant role is emerging for functional foods in cardiovascular prevention. The aim of this study was to assess the effect of a nutraceutical multitargeted approach on lipid profile and inflammatory markers along with vascular remodelling in a cohort of dyslipidemic subjects without history of cardiovascular (CV) disease. METHODS AND RESULTS: We enrolled 25 subjects (mean age 48.2 years) with low to moderate CV risk profile and total cholesterol (TC) levels between 150 and 250 mg/dl. The patients were assigned to receive for one year a tablet/die of a nutraceutical combination containing red yeast rice (RYR) extract (Monacolin 3 mg/tablet) and coenzyme Q10 (30 mg/tablet). Treatment with the nutraceutical compounds led to a significant reduction of TC (from 227 to 201 mg/dl, $p < 0.001$), LDL-c (from 150 to 130 mg/dl, $p = 0.001$), triglycerides (from 121 to 109 mg/dl, $p = 0.013$), non-HDL-cholesterol (from 168 to 141 mg/dl, $p < 0.001$), hs-CRP (from 1.74 to 1.20 mg/l, $p = 0.015$), and osteoprotegerin (from 1488 to 1328 pg/ml, $p = 0.045$). Levels of HDL-c, Lp(a), glucose, liver enzyme, CPK, or creatinine did not change over time. An ultrasound study was performed to assess changes in mean carotid intima-media thickness (IMT) and maximum IMT (M-MAX) as well as modification in local carotid stiffness by means of determining the carotid compliance coefficient (CC) and distensibility coefficient (DC). At the end of the treatment, we observed small but significant reductions in both mean-IMT (from 0.62 to 0.57 mm, $p = 0.022$) and M-MAX (from 0.79 to 0.73 mm, $p = 0.002$), and an improvement in carotid elasticity (DC from 22.4 to 24.3 × 10(-3)/kPa, $p = 0.006$ and CC from 0.77 to 0.85 mm(2)/kPa, $p = 0.019$). CONCLUSIONS: A

long-term treatment with a combination of RYR and coenzyme Q10 showed lipid-lowering activity along with a reduction of inflammatory mediators and an improvement of vascular properties in young subjects with a low-to-moderate CV risk profile.

[7] *Keech AC, Oyama K, Sever PS et al.* **Efficacy and Safety of Long-Term Evolocumab Use Among Asian Subjects - A Subgroup Analysis of the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) Trial**. Circulation journal : official journal of the Japanese Circulation Society 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33980763

ABSTRACT

BACKGROUND: There are concerns that Asian patients respond differently to some medications. This study evaluated the efficacy and safety of evolocumab among Asian vs. other subjects in the FOURIER trial, which randomized stable atherosclerosis patients to receive either evolocumab or placebo.Methods and Results:Effects of adding evolocumab vs. placebo to background statin therapy on low-density lipoprotein cholesterol (LDL-C) reductions, cardiovascular outcomes, and adverse events were compared among 27,564 participants with atherosclerotic disease, according to self-reported Asian (n=2,723) vs. other (n=24,841) races followed for a median of 2.2 years in the FOURIER trial. The primary endpoint was a composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. At randomization, Asians had slightly lower LDL-C (median 89 [IQR 78-104] mg/dL vs. 92 [80-109] mg/dL; P<0.001) and were much less likely to be on a high-intensity statin (33.3% vs. 73.3%; P<0.001). Evolocumab lowered LDL-C more in Asians than in others (66% vs. 58%; P<0.001). The effect of evolocumab on the primary endpoint was similar in Asians (HR, 0.79; 95% CI, 0.61-1.03) and others (HR, 0.86; 95% CI, 0.79-0.93; P interaction=0.55). There was no excess of serious adverse events with evolocumab among Asians over others. CONCLUSIONS: Use of evolocumab robustly lowers LDL-C and is equally efficacious in lowering the risk of cardiovascular events and safe in Asians as it is in others.

[8] *Amarenco P, Kim JS, Labreuche J et al.* **Impact of lower vs higher LDL cholesterol targets on cardiovascular events after ischemic stroke in diabetic patients**. Diabetes 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33980690

ABSTRACT

After an ischemic stroke with evidence of atherosclerosis, lipid lowering treatment with a target LDL cholesterol of less than 70 mg/dL compared to 100±10 mg/dL, reduced the risk of subsequent cardiovascular events. In this analysis, we explored the effect in the diabetic compared to nondiabetic subgroup and newly diagnosed diabetes.Patients with ischemic stroke in the previous 3 months or TIA within the previous 15 days and evidence of cerebrovascular or coronary artery atherosclerosis were randomly assigned in a 1:1 ratio to a target LDL cholesterol of less than 70 mg/dL or 100±10 mg/dL, using statin or ezetimibe. The primary outcome was the composite of ischemic stroke, myocardial infarction, new symptoms requiring urgent coronary or carotid revascularization and vascular death. We did a pre specified analysis to evaluate the effect in diabetic patients.Among 2,860 patients enrolled, 643 were diabetic at baseline with a mean age of 66.2 years and baseline LDL cholesterol of 127 mg/dL and were followed for a median of 3 years. The primary composite endpoint occurred in 27/328 (8.2%) patients in the lower target group and in 44/315 (14.0%) patients in the higher target group (adjusted hazard ratio, 0.56 [95% CI, 0.34 to 0.89]; P=0.016), while hazard

ratio was 0.87 (95% CI, 0.66 to 1.14; P=0.31) in nondiabetic patients (Pinteraction=0.15). In diabetics, there were 3 intracranial hemorrhages in both randomization groups (0.9% vs. 1.0%, respectively). Newly diagnosed diabetes occurred in 98/1070 (9.2%) and in 80/1085 (7.4%) patients in the lower and higher target group, respectively (HR=1.27 [95% CI, 0.94 to 1.71], P=0.11) and baseline higher HbAIc was the unique multivariable predictor.In conclusions, after an ischemic stroke with evidence of atherosclerosis, targeting an LDL cholesterol of less than 70 mg/dL compared to 100±10 mg/dL consistently reduced the risk of subsequent stroke and other major vascular events in diabetic and nondiabetic patients, but the higher risk in diabetic patients yielded a higher absolute risk reduction with an NNT of 17 (ClinicalTrials.gov NCT01252875- EUDRACT Identifier number 2009-A01280-57).

[9] *Ahmed AO, Okotcha E, Saad AH*. **Gemfibrozil-Induced Polyuria**. European journal of case reports in internal medicine 2021; 8:002546.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33987132
ABSTRACT
Gemfibrozil is a lipid-regulating agent used mainly to treat patients with hypertriglyceridaemia, especially those at risk for acute pancreatitis. Like any other pharmacological agent, gemfibrozil has known adverse effects, mainly gastrointestinal, such as cholelithiasis, gallstones, elevated transaminase, and other non-specific symptoms including dyspepsia, nausea and vomiting. Other reported adverse reactions are dizziness and vertigo, myopathy and rhabdomyolysis, angioedema, urticaria and rash. As far as we knew, gemfibrozil does not have urinary tract adverse reactions. In this report, we present a case of polyuria secondary to gemfibrozil with a score of 9 on the Naranjo scale, and a literature review. LEARNING POINTS: Gemfibrozil has known, mainly gastrointestinal, adverse effects.We aim to increase awareness of the urinary side effects of gemfibrozil so unnecessary investigations can be avoided.

[10] *Zeitlinger M, Bauer M, Reindl-Schwaighofer R et al.* **A phase I study assessing the safety, tolerability, immunogenicity, and low-density lipoprotein cholesterol-lowering activity of immunotherapeutics targeting PCSK9**. Eur J Clin Pharmacol 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33969434
ABSTRACT
PURPOSE: AT04A and AT06A are two AFFITOPE® peptide vaccine candidates being developed for the treatment of hypercholesterolemia by inducing proprotein convertase subtilisin/kexin type 9 (PCSK9)-specific antibodies. This study aimed to investigate safety, tolerability, antibody development, and reduction of low-density lipoprotein cholesterol (LDLc) following four subcutaneous immunizations. METHODS: This phase I, single-blind, randomized, placebo-controlled study was conducted in a total of 72 healthy subjects with a mean fasting LDLc level at baseline of 117.1 mg/dL (range 77-196 mg/dL). Each cohort enrolled 24 subjects to receive three priming immunizations at weeks 0, 4, and 8 and to receive a single booster immunization at week 60 of either AT04A, AT06A, or placebo. In addition to safety (primary objective), the antigenic peptide- and PCSK9-specific antibody response and the impact on LDLc were evaluated over a period of 90 weeks. RESULTS: The most common systemic treatment-related adverse events (AEs) reported were fatigue, headache, and myalgia in 75% of subjects in the AT06A group and 58% and 46% of subjects in the placebo and AT04A groups, respectively. Injection site reactions (ISR) representing 63% of all treatment-emergent adverse events (TEAEs), were transient and mostly of mild or moderate intensity

and rarely severe (3%). Both active treatments triggered a robust, long-lasting antibody response towards the antigenic peptides used for immunization that optimally cross-reacted with the target epitope on PCSK9. In the AT04A group, a reduction in serum LDLc was observed with a mean peak reduction of 11.2% and 13.3% from baseline compared to placebo at week 20 and 70 respectively, and over the whole study period, the mean LDLc reduction for the AT04A group vs. placebo was -7.2% (95% CI [-10.4 to -3.9], P<0.0001). In this group, PCSK9 target epitope titers above 50 were associated with clinically relevant LDLc reductions with an individual maximal decrease of 39%. CONCLUSIONS: Although both AT04A and AT06 were safe and immunogenic, only AT04A demonstrated significant LDLc-lowering activity, justifying further development. TRIAL REGISTRATION: EudraCT: 2015-001719-11. ClinicalTrials.gov Identifier: NCT02508896.

[11] *Shin J, Chung JW, Jang HS et al.* **Achieved low-density lipoprotein cholesterol level and stroke risk: A meta-analysis of 23 randomised trials**. European journal of preventive cardiology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33978157
ABSTRACT
AIMS: Lowering the low-density lipoprotein cholesterol level reduces the risk of stroke, but it has not been clear whether the stroke risk would continuously decrease by lowering low-density lipoprotein cholesterol to a very low level. The purpose of this study was to evaluate the association between achieved low-density lipoprotein cholesterol levels and stroke risk. METHODS AND RESULTS: A systematic search of MEDLINE, EMBASE and Cochrane Library databases was conducted to identify randomised controlled trials that tested cholesterol-lowering pharmacological therapies and reported both achieved low-density lipoprotein cholesterol levels and stroke outcomes. A meta-regression analysis was conducted to assess the linear association between the achieved low-density lipoprotein cholesterol levels and stroke risk. In addition, we evaluated pooled estimates of low-density lipoprotein cholesterol-lowering effect stratified by achieved low-density lipoprotein cholesterol levels of active arms. A total of 222,149 participants in 23 trials (52 arms of 26 studies) were included. The meta-regression analysis showed that each 1 mmol/L decrease in the achieved low-density lipoprotein cholesterol level (down to 0.78 mmol/L) was associated with a significant reduction of 23.5% (slope 0.235, 95% confidence interval 0.007-0.464, P = 0.044) in stroke risk. Irrespective of achieved low-density lipoprotein cholesterol levels in the active arms, the effects of lowering the low-density lipoprotein cholesterol level on stroke risk were significant and consistent (test for subgroup difference, P = 0.23, I2 = 31%). However, there was no significant increase in haemorrhagic stroke risk with lower achieved low-density lipoprotein cholesterol levels. CONCLUSION: In this meta-analysis of randomised controlled trials, the stroke risk monotonically reduced with lowering of low-density lipoprotein cholesterol to very low levels.

[12] *Ooi BNS, Raechell, Ying AF et al.* **Robust Performance of Potentially Functional SNPs in Machine Learning Models for the Prediction of Atorvastatin-Induced Myalgia**. Frontiers in pharmacology 2021; 12:605764.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33967749
ABSTRACT
Statins can cause muscle symptoms resulting in poor adherence to therapy and increased cardiovascular risk. We hypothesize that combinations of potentially functional SNPs (pfSNPs), rather

than individual SNPs, better predict myalgia in patients on atorvastatin. This study assesses the value of potentially functional single nucleotide polymorphisms (pfSNPs) and employs six machine learning algorithms to identify the combination of SNPs that best predict myalgia. Methods: Whole genome sequencing of 183 Chinese, Malay and Indian patients from Singapore was conducted to identify genetic variants associated with atorvastatin induced myalgia. To adjust for confounding factors, demographic and clinical characteristics were also examined for their association with myalgia. The top factor, sex, was then used as a covariate in the whole genome association analyses. Variants that were highly associated with myalgia from this and previous studies were extracted, assessed for potential functionality (pfSNPs) and incorporated into six machine learning models. Predictive performance of a combination of different models and inputs were compared using the average cross validation area under ROC curve (AUC). The minimum combination of SNPs to achieve maximum sensitivity and specificity as determined by AUC, that predict atorvastatin-induced myalgia in most, if not all the six machine learning models was determined. Results: Through whole genome association analyses using sex as a covariate, a larger proportion of pfSNPs compared to non-pf SNPs were found to be highly associated with myalgia. Although none of the individual SNPs achieved genome wide significance in univariate analyses, machine learning models identified a combination of 15 SNPs that predict myalgia with good predictive performance (AUC >0.9). SNPs within genes identified in this study significantly outperformed SNPs within genes previously reported to be associated with myalgia. pfSNPs were found to be more robust in predicting myalgia, outperforming non-pf SNPs in the majority of machine learning models tested. Conclusion: Combinations of pfSNPs that were consistently identified by different machine learning models to have high predictive performance have good potential to be clinically useful for predicting atorvastatin-induced myalgia once validated against an independent cohort of patients.

[13] *Marron MM, Moore SC, Wendell SG et al.* **Using lipid profiling to better characterize metabolic differences in apolipoprotein E (APOE) genotype among community-dwelling older Black men**. Geroscience 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33991295
ABSTRACT
Apolipoprotein E (APOE) allelic variation is associated with differences in overall circulating lipids and risks of major health outcomes. Lipid profiling provides the opportunity for a more detailed description of lipids that differ by APOE, to potentially inform therapeutic targets for mitigating higher morbidity and mortality associated with certain APOE genotypes. Here, we sought to identify lipids, lipid-like molecules, and important mediators of fatty acid metabolism that differ by APOE among 278 Black men ages 70-81. Using liquid chromatography-mass spectrometry methods, 222 plasma metabolites classified as lipids, lipid-like molecules, or essential in fatty acid metabolism were detected. We applied principal factor analyses to calculate a factor score for each main lipid category. APOE was categorized as ε4 carriers (n = 83; ε3ε4 or ε4ε4), ε2 carriers (n = 58; ε2ε3 or ε2ε2), or ε3 homozygotes (n = 137; ε3ε3). Using analysis of variance, the monoacylglycerol factor, cholesterol ester factor, the factor for triacylglycerols that consist mostly of polyunsaturated fatty acids, sphingosine, and free carnitine significantly differed by APOE ($p < 0.05$, false discovery rate < 0.30). The monoacylglycerol factor, cholesterol ester factor, and sphingosine were lower, whereas the factor for triacylglycerols that consisted mostly of polyunsaturated fatty acids was higher among ε2 carriers than remaining participants. Free carnitine was lower among ε4 carriers than ε3 homozygotes. Lower

monoacylglycerols and cholesteryl esters and higher triacylglycerols that consist mostly of polyunsaturated fatty acids may be protective metabolic characteristics of APOE ε2 carriers, whereas lower carnitine may reflect altered mitochondrial functioning among ε4 carriers in this cohort of older Black men.

[14] *Yamashita S, Masuda D, Harada-Shiba M et al.* **Effectiveness and Safety of Lipid-Lowering Drug Treatments in Japanese Patients with Familial Hypercholesterolemia: Familial Hypercholesterolemia Expert Forum (FAME) Study**. Journal of atherosclerosis and thrombosis 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33980760

ABSTRACT

AIMS: Familial hypercholesterolemia (FH) is a genetic disorder characterized by high serum levels of low-density lipoprotein (LDL)-cholesterol (LDL-C), tendon and skin xanthomas, and premature coronary artery disease (CAD). In Japan, detailed information on the current status of drug therapies for patients with FH has not been reported so far, and their efficacy and safety have not been clarified. After the introduction of ezetimibe, which can further reduce serum LDL-C levels on top of statins, the changes of management for FH patients with these drugs are of particular interest. The current study aimed to evaluate the clinical status of FH heterozygotes and homozygotes, especially focusing on the real-world lipid-lowering drug therapy, attained serum LDL-C levels, and cardiovascular events at registration and during the follow-up. METHODS: The FAME Study enrolled 762 heterozygous (including 17 newly diagnosed cases) and 7 homozygous FH patients from hospitals and clinics nationwide. Diagnosis of FH was based upon the criteria defined in the Study Report in 2008 of the Research Committee on Primary Hyperlipidemia supported by Grants-in-Aid for Scientific Research from the Japanese Ministry of Health, Labor and Welfare. Data analysis was primarily carried on heterozygous FH patients. RESULTS: Xanthoma or thickening of the Achilles tendon was observed in more than 80% of the patients. CAD was recorded in 23% of patients. Patients with parental and sibling CAD accounted for 47% and 24%, respectively. At baseline, patients without CAD who had LDL-C ＜100 mg/dL accounted for 12.3% and those with CAD who had attained the target (LDL-C ＜70 mg/dL) in the secondary prevention accounted for only 1.8%. In the multiple logistic analysis, male sex, age ＞40, heterozygous FH score ＞20, hypertension, and sibling CAD were significantly and positively associated with prevalent CAD, whereas serum HDL-cholesterol levels showed a significant inverse association with CAD. Patients treated with statin alone, statin＋ezetimibe, statin＋resin, or statin＋probucol accounted for 31.1%, 26.3%, 4.0%, and 3.7%, respectively. Patients treated with three-drug combination (statin＋ezetimibe＋resin or statin＋ezetimibe＋probucol) accounted for 7.5%. Statins and ezetimibe were used in 88.0% and 48.0% at the baseline, respectively. Although high-intensity statins were mainly prescribed, statin doses were much lower than those reported in Western countries. The addition of ezetimibe resulted in ~20% reduction in serum LDL-C. CAD was diagnosed in 17 patients with 21 episodes during follow-up. The Cox hazard model analysis demonstrated that male sex, CAD at the baseline, and parental CAD were related to the development of atherosclerotic cardiovascular disease (ASCVD) events. Furthermore, an increase in serum HDL-C was associated with a significant reduction of ASCVD

events, while serum LDL-C and triglyceride levels were not related to ASCVD events. CONCLUSION: The prevalence of CAD in Japanese patients with heterozygous FH is still very high. In most of the cases, the target level of serum LDL-C was not achieved for primary and secondary prevention of CAD, suggesting that a more aggressive LDL-C lowering and appropriate management of residual risks are necessary.

[15] *Warden BA, Duell PB*. **Inclisiran: A Novel Agent for Lowering Apolipoprotein B-Containing Lipoproteins**. Journal of cardiovascular pharmacology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33990512
ABSTRACT
Hypercholesterolemia is a leading cause of cardiovascular morbidity and mortality. Accordingly, efforts to lower apolipoprotein B-containing lipoproteins in plasma are the centerpiece of strategies for cardiovascular prevention and treatment in primary and secondary management. Despite the importance of this endeavor, many patients do not achieve appropriate low density lipoprotein cholesterol (LDL-C) and non-high density lipoprotein cholesterol (non-HDL-C) goals, even among those who have experienced atherosclerotic cardiovascular disease (ASCVD). The development of new LDL-C-lowering medications with alternative mechanisms of action will facilitate improved goal achievement in high risk patients. Inclisiran is a novel small interfering ribonucleic acid (siRNA)-based drug that is experimental in the US and approved for clinical use in the EU. It lowers LDL-C and other apolipoprotein B-containing lipoproteins by reducing production of Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9), a protein that normally contributes to LDL-receptor (LDLR) degradation, thereby increasing LDLR density and recycling in hepatocytes. Although the lipid-lowering efficacy of inclisiran is comparable to results achieved with PCSK9-blocking monoclonal antibodies (PCSK9i) (alirocumab and evolocumab), there are several important differences between the two drug classes. First, inclisiran reduces levels of PCSK9 both intracellularly and extracellularly by blocking translation of and degrading PCSK9 messenger RNA. Second, the long biological half-life of inclisiran produces sustained LDL-C-lowering with twice yearly dosing. Third, although PCSK9i drugs are proven to reduce ASCVD events, clinical outcomes trials with inclisiran are still in progress. In this manuscript, we review the clinical development of inclisiran, its mechanism of action, lipid-lowering efficacy, safety and tolerability, and potential clinical role of this promising new agent.

[16] *Allan S, Pencina M, Thanassoulis G*. **Clinical reasoning and prevention of cardiovascular disease**. Journal of clinical lipidology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33992590
ABSTRACT
All the major lipid prevention guidelines agree that the 10-year risk of a cardiovascular event should be the primary method to select individuals for statin prevention of a cardiovascular event. They also all rely on LDL cholesterol (LDL-C) as the primary metric to monitor lipid lowering therapy. These two principles form the major instruments on which primary prevention of cardiovascular disease is based worldwide. Their application is based on decades of prospective observational studies and large numbers of randomized clinical trials. Their development and application are milestones in medical progress. But are there limits, which were unseen and unintended, that need to be identified and overcome so that cardiovascular prevention can improve? Based on new insights and old knowledge, this Viewpoint will apply Clinical Reasoning, the process by which we integrate all the relevant

knowledge, including the knowledge we have gained from physiology, pathology, epidemiology, metabolism, experimental models of disease, and our clinical experience as well as the results of randomized clinical trials to the analysis of a single case to answer these questions. Moreover, this Viewpoint will challenge the universal practice of relating the clinical outcomes of the major successful lipid lowering trials to the decrease in LDL-C and argue that cardiovascular prevention should move from the Risk model to the Causal Benefit model. This Viewpoint will be framed around a single case because, as caregivers, we make decisions case by case and because, as caregivers, the individual is the true object of our concern.

[17] *Wu H, Wang C, Tuerhongjiang G et al.* **Circulating lipid and lipoprotein profiles and their correlation to cardiac function and cardiovascular outcomes in patients with acute myocardial infarction**. Journal of investigative medicine : the official publication of the American Federation for Clinical Research 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33972383

ABSTRACT

Recent studies showed that lipoproteins represent major risk factors, both positive and negative, for atherosclerotic cardiovascular disease. The aim of the present study was to describe the relationship between plasma lipid profile and cardiac function and cardiovascular outcomes in patients with acute myocardial infarction (AMI) after percutaneous coronary intervention (PCI). Two independent groups of subjects including a total of 797 patients diagnosed of AMI undergoing PCI admitted to the First Affiliated Hospital of Xi'an Jiaotong University were included in the present study. We performed a cross-sectional study for the correlation between plasma lipid profile and cardiac function based on the first group, including 503 patients with AMI. We further validated the correlation and did the follow-up of 2.4 years of major cardiovascular outcomes on the second group, including 294 patients with AMI. Our results showed that apolipoprotein A-I (ApoA-I) level was significantly reduced, and the high-density lipoprotein cholesterol (HDL-C):ApoA-I ratio was increased in the patients with lower LVEF or higher N-terminal pro-B-type natriuretic peptide levels compared with the control; there was a positive correlation between cardiac function and ApoA-I, and a negative correlation between cardiac function and the HDL-C:ApoA-I ratio. Meanwhile, multivariate Cox analysis showed that ApoA-I was independent predictors of major adverse cardiovascular events (MACEs). Kaplan-Meier survival analysis showed the ApoA-I levels exhibited a significant effect on predicting the incidence of MACEs. In sum, plasma ApoA-I level is positively associated with the cardiac function of patients with AMI after PCI, and ApoA-I is an independent indicator to predict the incidence of MACEs.

[18] *Zhu L, Liu J, Yu Y, Tian Z*. **Effect of high-intensity interval training on cardiometabolic risk factors in childhood obesity: a meta-analysis**. J Sports Med Phys Fitness 2021; 61:743-752.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33975429

ABSTRACT

INTRODUCTION: This systematic review with meta-analysis aimed to quantify the effectiveness of high-intensity interval training (HIIT) on the cardiometabolic health of obese children and adolescents. EVIDENCE ACQUISITION: Relevant articles were sourced from PubMed, Embase, the Web of Science, EBSCO, the Cochrane Library and China National Knowledge Infrastructure (CNKI). Randomized controlled trials were included if they employed participants aged 7-19 years. Outcomes included fasting glucose (FG), fasting insulin (FI), homeostasis model assessment-insulin resistance

(HOMA-IR), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), triacylglycerol (TG), total cholesterol (TC), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured at baseline and postintervention and compared with those in the control group. Data analysis and synthesis were completed by Revman 5.3 software and Stata 12.0 software (StataCorp LLC., College Station, TX, USA). EVIDENCE SYNTHESIS: Eight trials involving 379 participants were identified. HIIT significantly decreased the FI, HOMA-IR, TC, TG, LDL-c and SBP in participants with obesity. With regard to changes in blood glucose and lipids, participants who underwent HIIT showed great improvement in FI (mean difference: -3.09 μU/mL, 95% confidence interval [CI] -3.71 to -2.46, P<0.0001), HOMA-IR (mean difference: -0.64, 95% CI -0.82 to -0.46, P<0.0001), TG (mean difference: -0.21 mmol/L, 95% CI -0.31 to -0.10, P<0.0001) and LDL-c (mean difference: -0.35 mmol/L, 95% CI -0.48 to -0.22, P<0.001) than the control group. Similar results were found for SBP (mean difference: -3.61 mmHg, 95% CI -5.85 to -1.37, P=0.002). However, no significant differences in changes in FG, HDL-c and DBP were observed between HIIT and control groups. CONCLUSIONS: HIIT can produce a positive effect on cardiometabolic risk factors in obese children and adolescents. HIIT may be an alternative and effective training method for managing childhood obesity.

[19] **Evinacumab (Evkeeza) for homozygous familial hypercholesterolemia**. The Medical letter on drugs and therapeutics 2021; 63:66-67.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33976097
ABSTRACT

[20] *Talasaz AH, Sadeghipour P, Aghakouchakzadeh M et al.* **Lipid-Modulating Agents for Prevention or Treatment of COVID-19 in Randomized Trials**. medRxiv 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33972948
ABSTRACT
Coronavirus disease 2019 (COVID-19) is associated with systemic inflammation, endothelial activation, and multi-organ manifestations. Lipid modulating agents may be useful in treating patients with COVID-19. They may inhibit viral entry by lipid raft disruption or ameliorate the inflammatory response and endothelial activation. In addition, dyslipidemia with lower high-density lipoprotein cholesterol and higher triglycerides portends worse outcome in patients with COVID-19. Upon a systematic search, 40 RCTs with lipid modulating agents were identified, including 17 statin trials, 14 omega-3 fatty acids RCTs, 3 fibrates RCTs, 5 niacin RCTs, and 1 dalcetrapib RCT for management or prevention of COVID-19. This manuscript summarizes the ongoing or completed randomized controlled trials (RCTs) of lipid modulating agents in COVID-19 and the implications of these trials for patient management.

[21] *Soehnlein O, Libby P*. **Targeting inflammation in atherosclerosis - from experimental insights to the clinic**. Nature reviews. Drug discovery 2021:1-22.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33976384
ABSTRACT
Atherosclerosis, a dominant and growing cause of death and disability worldwide, involves inflammation from its inception to the emergence of complications. Targeting inflammatory pathways could therefore provide a promising new avenue to prevent and treat atherosclerosis. Indeed, clinical

studies have now demonstrated unequivocally that modulation of inflammation can forestall the clinical complications of atherosclerosis. This progress pinpoints the need for preclinical investigations to refine strategies for combatting inflammation in the human disease. In this Review, we consider a gamut of attractive possibilities for modifying inflammation in atherosclerosis, including targeting pivotal inflammatory pathways such as the inflammasomes, inhibiting cytokines, manipulating adaptive immunity and promoting pro-resolution mechanisms. Along with lifestyle measures, pharmacological interventions to mute inflammation could complement traditional targets, such as lipids and hypertension, to make new inroads into the management of atherosclerotic risk.

[22] *Ha HS, Kim TY, Han SJ et al.* **Anti-atherosclerotic vaccination against Porphyromonas gingivalis as a potential comparator of statin in mice**. PeerJ 2021; 9:e11293.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33976982

ABSTRACT

BACKGROUND: Porphyromonas gingivalis (Pg) is an oral anaerobe which damages teeth and periodontal tissues. Its body infection is known to cause chronic inflammation, thereby inducing an early stage of atherosclerosis through humoral immune actions. Hence, vaccination by immunizing the proteins of P. gingivalis (Pg) post sonication with heating may prevent atherosclerosis. This study aimed to compare the effect of its vaccination with statin, which effectively prevents atherosclerosis by lowering lipids. METHODS: The vaccine was produced by sonicating P. gingivalis through heating, and a total of 32 male APOE-/-mice (8-week old) were subjected Western diet for 8 weeks, in order to induce atherosclerosis in a physiological manner. Then, the mice were grouped to undergo four treatment conditions (i.e., no treatment, pitavastatin, vaccine, or pitavastatin with vaccine). Vaccination was conducted through nasal immunization and confirmed by a Pg-specific humoral immune reaction. Then, half of the mice in each group were orally injected with P. gingivalis for the next 5 weeks while the other half remained uninfected, generating a total of eight groups (n = 4/group). The mice were sacrificed at 3 weeks after the last injection. After harvesting the aorta, Oil Red O staining of en face was conducted with imaging and image analysis, and plaque formation was quantitatively determined. RESULTS: Compared to no treatment, the vaccination through nasal immunization significantly reduced the atherosclerotic plaque sizes in APOE -/- mice under Western diet to the comparable level of statin group. When both vaccine and statin were used, no clear synergistic effect was observed as opposed to expectation. CONCLUSIONS: This study revealed that nasal immunization of heat shock P. gingivalis has a significant impact on the prevention of arteriosclerosis and acts as a potential comparator of statin.

[23] *Škorňová I, Samoš M, Bolek T et al.* **Does atorvastatin therapy change the anti-Xa activity in xabans-treated patients with atrial fibrillation?** Pharmacol Res Perspect 2021; 9:e00730.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33984191

ABSTRACT

Atorvastatin and direct oral factor Xa inhibitors (xabans) are frequently co-administrated in patients with atrial fibrillation (AF). However, no studies investigating the possibility of the pharmacologic interaction between these agents have been conducted. The aim of this prospective observational study was to determine the impact of atorvastatin therapy on anti-Xa activity in xabans-treated patients with AF. We enrolled 115 AF patients on long-term rivaroxaban (52 patients) and long-term apixaban (63 patients) therapy. Long-term atorvastatin (40 mg once daily) was administrated to 28

rivaroxaban-treated patients and to 28 apixaban-treated patients. Trough and peak samples were tested for anti-Xa activity with drug-specific anti-Xa chromogenic analysis. For rivaroxaban, there were no significant differences in trough activity (45.5 ± 39.5 ng/ml vs. 46.2 ± 30.1 ng/ml; p = .34) and peak anti-Xa activity (179.2 ± 108.8 ng/ml vs. 208.1 ± 104.1 ng/ml; p = .94) between atorvastatin-treated patients and those without atorvastatin. Similarly, atorvastatin did not impact the trough activity (127.7 ± 71.1 ng/ml vs. 100.8 ± 61.1 ng/ml; p = .12) or peak anti-Xa activity (213.8 ± 103.6 ng/ml vs. 179.3 ± 72.9 ng/ml; p = .14) among apixaban-treated patients with AF. This observational study did not show a significant impact of atorvastatin on trough and peak anti-Xa activity in xabans-treated patients with AF.

[24] *Lee SE, Sung JM, Andreini D et al.* **Association between Aortic Valve Calcification Progression and Coronary Atherosclerotic Plaque Volume Progression in the PARADIGM Registry**. Radiology 2021:202630.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33973837

ABSTRACT

Background Aortic valve calcification (AVC) is a key feature of aortic stenosis, and patients with aortic stenosis often have coronary -artery disease. Therefore, proving the association between the progression of AVC and coronary atherosclerosis could improve follow-up and treatment strategies. Purpose To explore the association between the progression of AVC and the progression of total and plaque volume composition from a large multicenter registry of serial coronary CT angiographic examinations. Materials and Methods A prospective multinational registry (PARADIGM) of consecutive participants who underwent serial coronary CT angiography at intervals of every 2 years or more was performed (January 2003-December 2015). AVC and the total and plaque volume composition at baseline and follow-up angiography were quantitatively analyzed. Plaque volumes were normalized by using the mean total analyzed vessel length of the study population. Multivariable linear mixed-effects models were constructed. Results Overall, 594 participants (mean age ± standard deviation, 62 years ± 10; 330 men) were included (mean interval between baseline and follow-up angiography, 3.9 years ± 1.5). At baseline, the AVC score was 31 Agatston units ± 117, and the normalized total plaque volume at baseline was 122 mm(3) ± 219. After adjustment for age, sex, clinical risk factors, and medication use, AVC was independently associated with total plaque volume (standardized β = 0.24; 95% CI: 0.16, 0.32; P < .001) and both calcified (β = 0.26; 95% CI: 0.18, 0.34; P < .001) and noncalcified (β = 0.17; 95% CI: 0.08, 0.25; P < .001) plaque volumes at baseline. The progression of AVC was associated with the progression of total plaque volume (β = 0.13; 95% CI: 0.03, 0.22; P = .01), driven solely by calcified plaque volume (β = 0.24; 95% CI: 0.14, 0.34; P < .001) but not noncalcified plaque volumes (β = -0.06; 95% CI: -0.14, 0.03; P = .17). Conclusion The overall burden of coronary atherosclerosis was associated with aortic valve calcification at baseline. However, the progression of aortic valve calcification was associated with only the progression of calcified plaque volume but not with the -progression of noncalcified plaque volume. Clinical trial registration no. NCT02803411 ©RSNA, 2021 See also the editorial by Sinitsyn in this issue.

[25] *Cho IJ, Oh DH, Yoo J et al.* **Allopurinol ameliorates high fructose diet induced hepatic steatosis in diabetic rats through modulation of lipid metabolism, inflammation, and ER stress pathway**. Scientific reports 2021; 11:9894.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33972568

ABSTRACT
Excess fructose consumption contributes to development obesity, metabolic syndrome, and nonalcoholic fatty liver disease (NAFLD). Uric acid (UA), a metabolite of fructose metabolism, may have a direct role in development of NAFLD, with unclear mechanism. This study aimed to evaluate role of fructose and UA in NAFLD and explore mechanisms of allopurinol (Allo, a UA lowering medication) on NAFLD in Otsuka Long-Evans Tokushima Fatty (OLETF) rats fed a high fructose diet (HFrD), with Long-Evans Tokushima Otsuka (LETO) rats used as a control. There were six groups: LETO, LETO-Allo, OLETF, OLETF-Allo, OLETF-HFrD, and OLETF-HFrD-Allo. HFrD significantly increased body weight, epididymal fat weight, and serum concentrations of UA, cholesterol, triglyceride, HbA1c, hepatic enzymes, HOMA-IR, fasting insulin, and two hour-glucose after intraperitoneal glucose tolerance tests, as well as NAFLD activity score of liver, compared to the OLETF group. Allopurinol treatment significantly reduced hepatic steatosis, epididymal fat, serum UA, HOMA-IR, hepatic enzyme levels, and cholesterol in the OLETF-HFrD-Allo group. Additionally, allopurinol significantly downregulated expression of lipogenic genes, upregulated lipid oxidation genes, downregulated hepatic pro-inflammatory cytokine genes, and decreased ER-stress induced protein expression, in comparison with the OLETF-HFrD group. In conclusion, allopurinol ameliorates HFrD-induced hepatic steatosis through modulation of hepatic lipid metabolism, inflammation, and ER stress pathway. UA may have a direct role in development of fructose-induced hepatic steatosis, and allopurinol could be a candidate for prevention or treatment of NAFLD.

[26] *Gennemark P, Walter K, Clemmensen N et al.* **An oral antisense oligonucleotide for PCSK9 inhibition**. Science translational medicine 2021; 13.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33980578

ABSTRACT
Inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9) reduce low-density lipoprotein (LDL) cholesterol and are used for treatment of dyslipidemia. Current PCSK9 inhibitors are administered via subcutaneous injection. We present a highly potent, chemically modified PCSK9 antisense oligonucleotide (ASO) with potential for oral delivery. Past attempts at oral delivery using earlier-generation ASO chemistries and transient permeation enhancers provided encouraging data, suggesting that improving potency of the ASO could make oral delivery a reality. The constrained ethyl chemistry and liver targeting enabled by N-acetylgalactosamine conjugation make this ASO highly potent. A single subcutaneous dose of 90 mg reduced PCSK9 by >90% in humans with elevated LDL cholesterol and a monthly subcutaneous dose of around 25 mg is predicted to reduce PCSK9 by 80% at steady state. To investigate the feasibility of oral administration, the ASO was coformulated in a tablet with sodium caprate as permeation enhancer. Repeated oral daily dosing in dogs resulted in a bioavailability of 7% in the liver (target organ), about fivefold greater than the plasma bioavailability. Target engagement after oral administration was confirmed by intrajejunal administration of a rat-specific surrogate ASO in solution with the enhancer to rats and by plasma PCSK9 and LDL cholesterol lowering in cynomolgus monkey after tablet administration. On the basis of an assumption of 5% liver bioavailability after oral administration in humans, a daily dose of 15 mg is predicted to reduce circulating PCSK9 by 80% at steady state, supporting the development of the compound for oral administration to treat dyslipidemia.

[27] *Bosch J, Lonn EM, Dagenais GR et al.* **Antihypertensives and Statin Therapy for Primary Stroke Prevention: A Secondary Analysis of the HOPE-3 Trial**. Stroke 2021:Strokeaha120030790.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33985364

ABSTRACT

BACKGROUND AND PURPOSE: The HOPE-3 trial (Heart Outcomes Prevention Evaluation-3) found that antihypertensive therapy combined with a statin reduced first stroke among people at intermediate cardiovascular risk. We report secondary analyses of stroke outcomes by stroke subtype, predictors, treatment effects in key subgroups. METHODS: Using a 2-by-2 factorial design, 12 705 participants from 21 countries with vascular risk factors but without overt cardiovascular disease were randomized to candesartan 16 mg plus hydrochlorothiazide 12.5 mg daily or placebo and to rosuvastatin 10 mg daily or placebo. The effect of the interventions on stroke subtypes was assessed. RESULTS: Participants were 66 years old and 46% were women. Baseline blood pressure (138/82 mm Hg) was reduced by 6.0/3.0 mm Hg and LDL-C (low-density lipoprotein cholesterol; 3.3 mmol/L) was reduced by 0.90 mmol/L on active treatment. During 5.6 years of follow-up, 169 strokes occurred (117 ischemic, 29 hemorrhagic, 23 undetermined). Blood pressure lowering did not significantly reduce stroke (hazard ratio [HR], 0.80 [95% CI, 0.59-1.08]), ischemic stroke (HR, 0.80 [95% CI, 0.55-1.15]), hemorrhagic stroke (HR, 0.71 [95% CI, 0.34-1.48]), or strokes of undetermined origin (HR, 0.92 [95% CI, 0.41-2.08]). Rosuvastatin significantly reduced strokes (HR, 0.70 [95% CI, 0.52-0.95]), with reductions mainly in ischemic stroke (HR, 0.53 [95% CI, 0.37-0.78]) but did not significantly affect hemorrhagic (HR, 1.22 [95% CI, 0.59-2.54]) or strokes of undetermined origin (HR, 1.29 [95% CI, 0.57-2.95]). The combination of both interventions compared with double placebo substantially and significantly reduced strokes (HR, 0.56 [95% CI, 0.36-0.87]) and ischemic strokes (HR, 0.41 [95% CI, 0.23-0.72]). CONCLUSIONS: Among people at intermediate cardiovascular risk but without overt cardiovascular disease, rosuvastatin 10 mg daily significantly reduced first stroke. Blood pressure lowering combined with rosuvastatin reduced ischemic stroke by 59%. Both therapies are safe and generally well tolerated. REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT00468923.