

Literature update week 48 (2018)

[1] *Su J, Fang M, Tian B et al. Atorvastatin protects cardiac progenitor cells from hypoxia-induced cell growth inhibition via MEG3/miR-22/HMGB1 pathway. Acta biochimica et biophysica Sinica 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30481260>

ABSTRACT

Heart failure (HF) induced by ischemia myocardial infarction (MI) is one of the major causes of morbidity and mortality all around the world. Atorvastatin, a hydroxymethylglutaryl coenzyme A reductase inhibitor, has been demonstrated to benefit patients with ischemic or non-ischemic-induced HF, but the mechanism is still poorly understood. Increasing evidence indicates that lncRNAs play important role in variety of human disease. However, the role and underlying molecular mechanisms remain largely unclear. In our work, we applied 0.5% O₂ to generate a hypoxia cardiac progenitor cell (CPC) model. Then, CCK8 and EdU assays were employed to investigate the role of atorvastatin in hypoxia CPC cell model. We found that hypoxia inhibits CPC viability and proliferation through modulating MEG3 expression, while atorvastatin application can protect CPCs from hypoxia-induced injury through inhibiting MEG3 expression. Then, we demonstrated that repression of MEG3 inhibited the hypoxia-induced injury of CPCs and overexpression of MEG3 inhibited the protective effect of atorvastatin in the hypoxia-induced injury of CPCs. Furthermore, our study illustrated that atorvastatin played its role in CPC viability and proliferation by modulating the expression of HMGB1 through the MEG3/miR-22 pathway. Our study, for the first time, uncovered the molecular mechanism of atorvastatin's protective role in cardiomyocytes under hypoxia condition, which may provide an exploitable target in developing effective therapy drugs for MI patients.

[2] *Pisarik P. Evidence Supporting Niacin Therapy Is More Nuanced Than Article States. American family physician 2018; 98:630-631.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30485053>

ABSTRACT

[3] *Wojcik C. Does Niacin Have Cardiovascular Benefits in Patients with Dyslipidemia? American family physician 2018; 98:631-632.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30485054>

ABSTRACT

[4] *De Nisco G, Kok AM, Chiastra C et al. The Atheroprotective Nature of Helical Flow in Coronary Arteries. Annals of biomedical engineering 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30488307>

ABSTRACT

Arterial hemodynamics is markedly characterized by the presence of helical flow patterns. Previous observations suggest that arterial helical blood flow is of physiological significance, and that its quantitative analysis holds promise for clinical applications. In particular, it has been reported that distinguishable helical flow patterns are potentially atheroprotective in the carotid bifurcation as they suppress flow disturbances. In this context, there is a knowledge gap about the physiological significance of helical flow in coronary arteries, a prominent site of atherosclerotic plaque formation. This study aimed at the quantitative assessment of helical

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blood flow in coronary arteries, and to investigate its possible associations with vascular geometry and with atherogenic wall shear stress (WSS) phenotypes in a representative sample of 30 swine coronary arteries. This study demonstrates that in coronary arteries: (1) the hemodynamics is characterized by counter-rotating bi-helical flow structures; (2) unfavorable conditions of WSS are strongly and inversely associated with helicity intensity ($r = -0.91$; $p < 0.001$), suggesting an atheroprotective role for helical flow in the coronary tree; (3) vascular torsion dictates helical flow features ($r = 0.64$; $p < 0.001$). The findings of this work support future studies on the role of helical flow in atherogenesis in coronary arteries.

[5] Guo M, Cai Y, He C, Li Z. **Coupled Modeling of Lipid Deposition, Inflammatory Response and Intraplaque Angiogenesis in Atherosclerotic Plaque.** *Annals of biomedical engineering* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30488310>

ABSTRACT

We propose a multiphysical mathematical model by fully coupling lipid deposition, monocytes/macrophages recruitment and angiogenesis to investigate the pathophysiological responses of an atherosclerotic plaque to the dynamic changes in the microenvironment. The time evolutions of cellular (endothelial cells, macrophages, smooth muscle cells, etc.) and acellular components (low density lipoprotein, proinflammatory cytokines, extravascular plasma concentration, etc.) within the plaque microenvironment are assessed quantitatively. The thickening of the intima, the distributions of the lipid and inflammatory factors, and the intraplaque hemorrhage show a qualitative consistency with the MRI and histology data. Models with and without angiogenesis are compared to demonstrate the important role of neovasculature in the accumulation of blood-borne components in the atherosclerotic lesion by extravasation from the leaky vessel wall, leading to the formation of a lipid core and an inflammatory microenvironment, which eventually promotes plaque destabilization. This model can serve as a theoretical platform for the investigation of the pathological mechanisms of plaque progression and may contribute to the optimal design of atherosclerosis treatment strategies, such as lipid-lowering or anti-angiogenetic therapies.

[6] Londregan AT, Aspnes G, Limberakis C et al. **Discovery of N-(piperidin-3-yl)-N-(pyridin-2-yl)piperidine/piperazine-1-carboxamides as small molecule inhibitors of PCSK9.** *Bioorganic & medicinal chemistry letters* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30482620>

ABSTRACT

A series of N-(piperidin-3-yl)-N-(pyridin-2-yl)piperidine/piperazine-1-carboxamides were identified as small molecule PCSK9 mRNA translation inhibitors. Analogues from this new chemical series, such as 4d and 4g, exhibited improved PCSK9 potency, ADME properties, and in vitro safety profiles when compared to earlier lead structures.

[7] Karlsson SA, Franzen S, Svensson AM et al. **Prescription of lipid-lowering medications for patients with type 2 diabetes mellitus and risk-associated LDL cholesterol: a nationwide study of guideline adherence from the Swedish National Diabetes Register.** *BMC Health Serv Res* 2018; 18:900.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30486824>

ABSTRACT

BACKGROUND: Management of type 2 diabetes mellitus (T2DM) encompasses intensive glycaemic control, along with treatment of comorbidities and complications to handle the increased risk of cardiovascular disease (CVD). Improved control of LDL-cholesterol (LDL-C) with lipid-lowering medications is associated with reduced CVD risk in T2DM patients. Thus, treatment guidelines recommend lipid-lowering medications for T2DM patients with LDL-C above risk-associated thresholds. This study aimed to assess healthcare provider adherence to guidelines regarding lipid-lowering medication prescription among T2DM patients and to analyse factors associated with lipid-lowering medication prescription. **METHODS:** Observations in 2007 - 2014 for T2DM patients age ≥ 18 were collected from the Swedish National Diabetes Register. Observations were excluded if they lacked information about LDL-C, lipid-lowering medication prescription or CVD. Observations with established CVD were attributed to secondary prevention; remaining observations were attributed to primary prevention. The analyses included primary and secondary prevention observations with LDL-C above risk-associated thresholds (LDL-C ≥ 2.5 mmol/l and LDL-C ≥ 1.8 mmol/l respectively). Guideline adherence was analysed as the probability of prescribing lipid-lowering medications using mixed-effect model regression adjusted for potential confounders. Factors associated with prescribing lipid-lowering medications were analysed for patient and healthcare provider characteristics using mixed-effect model regression and odds ratio. **RESULTS:** A total of 1,204,376 observations from 322,046 patients reported by 1352 healthcare providers were included. Primary prevention accounted for 63%; 52% were men, mean age was 64 and mean LDL-C was 3.4 mmol/l. For secondary prevention, 60% were men, mean age was 72 and mean LDL-C was 2.7 mmol/l. During 2007-2014, guideline adherence ranged from 36 to 47% for primary prevention and 59 to 69% for secondary prevention. In general, concomitant prescription of diabetes medications, antiplatelets and antihypertensives along with smoking and specialised care were associated with higher prescription of lipid-lowering medications. Patients age ≥ 80 were associated with lower prescription of lipid-lowering medications. Higher prescription was associated with longer diabetes duration in primary prevention and men in secondary prevention. **CONCLUSIONS:** Adherence to treatment guidelines levelled off after an initial increase in both prevention groups. Lipid-lowering medication prescription was based on individualised CVD risk.

[8] Cimmino G, Cirillo P. **Tissue factor: newer concepts in thrombosis and its role beyond thrombosis and hemostasis.** *Cardiovascular diagnosis and therapy* 2018; 8:581-593.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30498683>

ABSTRACT

For many years, the attention on tissue factor (TF) in human pathophysiology has been limited to its role as initiator of extrinsic coagulation pathway. Moreover, it was described as a glycoprotein located in several tissue including vascular wall and atherosclerotic plaque. However, in the last two decades, the discovery that TF circulates in the blood as cell-associated protein, microparticles (MPs) bound and as soluble form, is changing this old vessel-wall TF dogma. Moreover, it has been reported that TF is expressed by different cell types, even T lymphocytes and platelets, and different pathological conditions, such as acute and chronic inflammatory status, and cancer, may enhance its expression and activity. Thus, recent

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advances in the biology of TF have clearly indicated that beyond its known effects on blood coagulation, it is a "true surface receptor" involved in many intracellular signaling, cell-survival, gene and protein expression, proliferation, angiogenesis and tumor metastasis. Finally, therapeutic modulation of TF expression and/or activity has been tested with controversial results. This report, starting from the old point of view about TF as initiator of extrinsic coagulation pathway, briefly illustrates the more recent concepts about TF and thrombosis and finally gives an overview about its role beyond thrombosis and haemostasis focusing on the different intracellular mechanisms triggered by its activation and potentially involved in atherosclerosis.

[9] *Lu YW, Lu SF, Chou RH et al. Lipid paradox in patients with acute myocardial infarction: Potential impact of malnutrition. Clinical nutrition (Edinburgh, Scotland) 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30482563>

ABSTRACT

BACKGROUND & AIMS: Aggressive lipid reduction is recommended for patients with AMI, but reverse epidemiology, the lipid paradox, has been reported in several clinical studies. The cause of lipid paradox remains uncertain, and nutrition is one possible explanation. In this single-center retrospective study, we investigated the relationships between baseline LDL concentrations and clinical outcomes in patients with AMI, stratified by different nutritional status. **METHODS:** Totally 409 patients were enrolled for analysis. The Nutritional Risk Index (NRI) was used to estimate the risk of malnutrition. Subjects were grouped into tertiles according to their NRIs. Clinical outcomes were compared among patients with varying NRIs and LDL levels. **RESULTS:** Patients in the lowest NRI tertile had increased incidences of in-hospital mortality, cardiogenic shock, decompensated heart failure, renal failure, and sepsis. This tertile was also associated with increased long-term mortality during the follow-up period of 832 +/- 744 days. Mortality was increased among patients with baseline LDL concentrations ≤ 70 mg/dL in the lowest NRI tertile (log rank test, $p = 0.0257$), but not in the high or median tertiles. Moreover, baseline LDL level ≤ 70 mg/dL was an independent risk factor of all-cause mortality (adjusted hazard ratio = 1.73; 95% confidence interval, 1.01-2.94; $p = 0.045$) in the lowest NRI tertile. **CONCLUSIONS:** Lipid paradox was observed in the high-risk of malnutrition population among patients with AMI. Aggressive lipid-lowering therapy is still recommended for patients with AMI and fair nutritional status. However, when treating patients at high risk of malnutrition, the improvement of nutritional status may be more beneficial than strict LDL control.

[10] *Heeney SA, Tjugum SL, Corkish ME, Hollis IB. Safety and tolerability of high intensity statin therapy in heart transplant patients receiving immunosuppression with tacrolimus. Clinical transplantation 2018:e13454.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30485535>

ABSTRACT

BACKGROUND: Following heart transplantation (HT), HMG CoA reductase inhibitors (statins) have been shown to reduce total and low-density lipoprotein (LDL) cholesterol, development of cardiac allograft vasculopathy (CAV), and mortality. Studies in HT patients have demonstrated the safety of low/moderate intensity statins, however little data exists using high intensity (HI)

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statins. The study aim was to evaluate the safety and efficacy of HI statins in HT recipients receiving tacrolimus. **METHODS:** This single center, retrospective analysis included adult HT recipients from January 1, 2005 to December 31, 2015 who received HI statin therapy during post-transplant follow-up. The primary outcome, tolerability, was defined as the absence of myalgias, hepatotoxicity, rhabdomyolysis, or HI statin dose reduction/discontinuation. The secondary end point was the mean reduction in total and LDL cholesterol. **RESULTS:** Among the 24 patients included, one experienced myalgias and therapy discontinuation (4%; $p>0.99$). No other HI statin dose reduction/discontinuation occurred, and no instances of rhabdomyolysis or hepatotoxicity were observed. The average reduction in total and LDL cholesterol after conversion to HI statin was 35 mg/dL ($p=0.02$) and 19 mg/dL ($p=0.10$), respectively. **CONCLUSIONS:** HI statin therapy appears safe and efficacious in HT recipients receiving tacrolimus and is a reasonable option for treatment of refractory hyperlipidemia. This article is protected by copyright. All rights reserved.

[11] Zhan S, Tang M, Liu F et al. **Ezetimibe for the prevention of cardiovascular disease and all-cause mortality events.** The Cochrane database of systematic reviews 2018; 11: Cd012502.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30480766>

ABSTRACT

BACKGROUND: Cardiovascular disease (CVD) remains an important cause of mortality and morbidity, and high levels of blood cholesterol are thought to be the major modifiable risk factors for CVD. The use of statins is the preferred treatment strategy for the prevention of CVD, but some people at high-risk for CVD are intolerant to statin therapy or unable to achieve their treatment goals with the maximal recommended doses of statin. Ezetimibe is a selective cholesterol absorption inhibitor, whether it has a positive effect on CVD events remains uncertain. Results from clinical studies are inconsistent and a thorough evaluation of its efficacy and safety for the prevention of CVD and mortality is necessary. **OBJECTIVES:** To assess the efficacy and safety of ezetimibe for the prevention of CVD and all-cause mortality. **SEARCH METHODS:** We searched the CENTRAL, MEDLINE, Embase and Web of Science on 27 June 2018, and two clinical trial registry platforms on 11 July 2018. We checked reference lists from primary studies and review articles for additional studies. No language restrictions were applied. **SELECTION CRITERIA:** We included randomised controlled trials (RCTs) that compared ezetimibe versus placebo or ezetimibe plus other lipid-modifying drugs versus other lipid-modifying drugs alone in adults, with or without CVD, and which had a follow-up of at least 12 months. **DATA COLLECTION AND ANALYSIS:** Two review authors independently selected studies for inclusion, extracted data, assessed risk of bias and contacted trialists to obtain missing data. We performed statistical analyses according to the Cochrane Handbook for Systematic Reviews of Interventions and used the GRADE to assess the quality of evidence. **MAIN RESULTS:** We included 26 RCTs randomising 23,499 participants. All included studies assessed effects of ezetimibe plus other lipid-modifying drugs compared with other lipid-modifying drugs alone or plus placebo. Our findings were driven by the largest study (IMPROVE-IT), which had weights ranging from 41.5% to 98.4% in the different meta-analyses. Ezetimibe with statins probably reduces the risk of major adverse cardiovascular events compared with statins alone (risk ratio (RR) 0.94, 95% confidence interval (CI) 0.90 to 0.98; a decrease from 284/1000 to 267/1000, 95% CI 256 to 278; 21,727 participants; 10 studies; moderate-quality evidence). Trials reporting

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all-cause mortality used ezetimibe with statin or fenofibrate and found they have little or no effect on this outcome (RR 0.98, 95% CI 0.91 to 1.05; 21,222 participants; 8 studies; high-quality evidence). Adding ezetimibe to statins probably reduces the risk of non-fatal myocardial infarction (MI) (RR 0.88, 95% CI 0.81 to 0.95; a decrease from 105/1000 to 92/1000, 95% CI 85 to 100; 21,145 participants; 6 studies; moderate-quality evidence) and non-fatal stroke (RR 0.83, 95% CI 0.71 to 0.97; a decrease 32/1000 to 27/1000, 95% CI 23 to 31; 21,205 participants; 6 studies; moderate-quality evidence). Trials reporting cardiovascular mortality added ezetimibe to statin or fenofibrate, probably having little or no effect on this outcome (RR 1.00, 95% CI 0.89 to 1.12; 19457 participants; 6 studies; moderate-quality evidence). The need for coronary revascularisation might be reduced by adding ezetimibe to statin (RR 0.94, 95% CI 0.89 to 0.99; a decrease from 196/1000 to 184/1000, 95% 175 to 194; 21,323 participants; 7 studies); however, no difference in coronary revascularisation rate was observed when a sensitivity analysis was limited to studies with a low risk of bias. In terms of safety, adding ezetimibe to statins may make little or no difference in the risk of hepatopathy (RR 1.14, 95% CI 0.96 to 1.35; 20,687 participants; 4 studies; low-quality evidence). It is uncertain whether ezetimibe increase or decrease the risk of myopathy (RR 1.31, 95% CI 0.72 to 2.38; 20,581 participants; 3 studies; very low-quality evidence) and rhabdomyolysis, given the wide CIs and low event rate. Little or no difference in the risk of cancer, gallbladder-related disease and discontinuation due to adverse events were observed between treatment groups. For serum lipids, adding ezetimibe to statin or fenofibrate might further reduce the low-density lipoprotein cholesterol (LDL-C), total cholesterol and triglyceride levels and likely increase the high-density lipoprotein cholesterol levels; however, substantial heterogeneity was detected in most analyses. None of the included studies reported on health-related quality of life.

AUTHORS' CONCLUSIONS: Moderate- to high-quality evidence suggests that ezetimibe has modest beneficial effects on the risk of CVD endpoints, primarily driven by a reduction in non-fatal MI and non-fatal stroke, but it has little or no effect on clinical fatal endpoints. The cardiovascular benefit of ezetimibe might involve the reduction of LDL-C, total cholesterol and triglycerides. There is insufficient evidence to determine whether ezetimibe increases the risk of adverse events due to the low and very low quality of the evidence. The evidence for beneficial effects was mainly obtained from individuals with established atherosclerotic cardiovascular disease (ASCVD, predominantly with acute coronary syndrome) administered ezetimibe plus statins. However, there is limited evidence regarding the role of ezetimibe in primary prevention and the effects of ezetimibe monotherapy in the prevention of CVD, and these topics thus requires further investigation.

[12] *Leiter LA, Teoh H, Kallend D et al. Inclisiran Lowers LDL-C and PCSK9 Irrespective of Diabetes Status: The ORION-1 Randomized Clinical Trial. Diabetes Care* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30487231>

ABSTRACT

OBJECTIVE: To evaluate the efficacy and safety of inclisiran by diabetes status. **RESEARCH DESIGN AND METHODS:** ORION-1 (ClinicalTrials.gov, NCT02597127) randomized 501 subjects with atherosclerotic cardiovascular disease (ASCVD) or ASCVD risk equivalents and high LDL cholesterol (LDL-C), despite maximally tolerated LDL-C-lowering therapies, to one or two doses of placebo or inclisiran. Levels of lipids and proprotein convertase subtilisin/kexin type 9

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(PCSK9) at baseline and day 180 were compared. RESULTS: Inclisiran was associated with marked declines in LDL-C (median -28% to -52%, $P < 0.0001$ and -28% to -55%, $P < 0.005$ for all doses in the without- and with-diabetes groups, respectively) and PCSK9. The inclisiran-treated groups also had lower apolipoprotein B, non-HDL cholesterol, and lipoprotein(a) but higher HDL cholesterol. Inclisiran had an adverse profile similar to that of placebo, and adverse events were proportionally balanced in the baseline with- and without-diabetes groups. CONCLUSIONS: PCSK9-targeted siRNA-driven strategies may provide a novel therapeutic option for managing dyslipidemia in the presence and absence of diabetes.

[13] *Monami M, Sesti G, Mannucci E. PCSK9 Inhibitor Therapy: A Systematic Review And Meta-Analysis of Metabolic And Cardiovascular Outcomes in Patients With Diabetes. Diabetes Obes Metab* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30485622>

ABSTRACT

AIM: Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors determine a wide reduction of LDL cholesterol, greater than other lipid-lowering agents. Aim of this metanalysis was the assessment of PCSK9 inhibitors effects on glucose metabolism, LDL-cholesterol, cardiovascular morbidity and mortality in patients with and without diabetes. METHODS: A Medline and Clinicaltrials.gov search for eligible studies until December 1(st) , 2017, was performed. All randomized trials comparing PCSK-9 inhibitors with placebo or active drugs were included. Primary endpoints: a) incident diabetes, fasting glucose and HbA1c; b) LDL-cholesterol at endpoint in patients with diabetes and in the total sample; c) MACE (major cardiovascular events) and mortality in patients with and without diabetes. RESULTS: A total of 38 trials was identified. The risk of incident diabetes was not increased by PCSK-9 inhibitors, either versus placebo or any comparator. The reduction of LDL-cholesterol versus placebo in patients with diabetes was 52.6[41.3;63.8]mg/dl; the corresponding figure for all patients was 66.9[62.4;71.3]mg/dl. Metaregression analysis showed an inverse correlation between proportion of patients with diabetes and drug effect on LDL cholesterol in trials versus ezetimibe, but not in those versus placebo. In studies reporting data on MACE and mortality separately for patients with and without diabetes, the effect of PCSK-9 did not appear to be affected by diabetes. CONCLUSIONS: PCSK-9 inhibitors does not affect glucose metabolism. Their efficacy on LDL-cholesterol and MACE in patients with diabetes does not seem to be very dissimilar from that observed in non-diabetic subjects. This article is protected by copyright. All rights reserved.

[14] *Genga KR, Lo C, Cirstea MS et al. Impact of PCSK9 loss-of-function genotype on 1-year mortality and recurrent infection in sepsis survivors. EBioMedicine* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30473376>

ABSTRACT

BACKGROUND: Reduced activity of proprotein convertase subtilisin/kexin type 9 (PCSK9) has been associated with decreased short-term death in patients with septic shock. Whether PCSK9 genotype influences long-term outcomes in sepsis survivors is unknown. METHODS: We evaluated the impact of PCSK9 loss-of-function (LOF) genotype on both 1-year mortality and infection-related readmission (IRR) after an index sepsis admission. The Derivation cohort

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included 342 patients who survived 28 days after a sepsis admission in a tertiary hospital (Vancouver/Canada, 2004-2014), while an independent Validation cohort included 1079 septic shock patients admitted at the same hospital (2000-2006). All patients were genotyped for three common missense PCSK9 LOF variants rs11591147, rs11583680, rs562556 and were classified in 3 groups: Wildtype, single PCSK9 LOF, and multiple PCSK9 LOF, according to the number of LOF alleles per patient. We also performed a meta-analysis using both cohorts to investigate the effects of PCSK9 genotype on 90-day survival. FINDINGS: In the Derivation cohort, patients carrying multiple PCSK9 LOF alleles showed lower risk for the composite outcome 1-year death or IRR (HR: 0.40, P=0.006), accelerated reduction on neutrophil counts (P=0.010), and decreased levels of PCSK9 (P=0.037) compared with WT/single LOF groups. Our meta-analysis revealed that the presence of multiple LOF alleles was associated with lower 90-day mortality risk (OR=0.69, P=0.020). INTERPRETATION: The presence of multiple PCSK9 LOF alleles decreased the risk of 1-year death or IRR in sepsis survivors. Biological measures suggest this may be related to an enhanced resolution of the initial infection. FUNDING: Canadian Institutes of Health Research (PJT-156056).

[15] *Yubero-Serrano EM, Lopez-Moreno J, Gomez-Delgado F, Lopez-Miranda J. Extra virgin olive oil: More than a healthy fat. European journal of clinical nutrition* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30487558>

ABSTRACT

The beneficial effects of a Mediterranean diet on human health and, in particular, on lowering risk of cardiovascular disease, has been mainly attributed to its high content to extra virgin olive oil (EVOO). While its main fatty acid, oleic acid, is considered important to these effects, EVOO has other biological properties that depend on, or are potentiated by other minor components of this oil. Initially, the mechanisms considered as possible causes of this cardioprotective effect of EVOO were based on the incidence on the so-called traditional risk factors (especially lipids and blood pressure). However, the high relative reduction in the prevalence of cardiovascular morbidity and mortality were not proportional to the limited findings about regulation of those traditional risk factors. In addition to several studies confirming the above effects, current research on beneficial effect of EVOO, and in particular in conjunction with Mediterranean style diets, is being focused on defining its effects on newer cardiovascular risk factors, such as inflammation, oxidative stress, coagulation, platelet aggregation, fibrinolysis, endothelial function or lipids or on the modulation of the conditions which predispose people to cardiovascular events, such as obesity, metabolic syndrome or type 2 diabetes mellitus. In the current review, we will mainly focus on reviewing the current evidence about the effects that EVOO exerts on alternative factors, including postprandial lipemia or coagulation, among others, discussing the underlying mechanism by which it exerts its effect, as well as providing a short review on future directions.

[16] *Chen X, Zhuang X, Peng Z et al. Intensive Statin Therapy for Acute Ischemic Stroke to Reduce the Number of Microemboli: A Preliminary, Randomized Controlled Study. European neurology* 2018; 80:163-170.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30485853>

ABSTRACT

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BACKGROUND: To assess whether intensive statin therapy reduces the occurrence of microemboli in patients with acute ischemic stroke. **METHODS:** Patients with acute ischemic stroke within 72 h of onset were randomized to the intensive statin (atorvastatin 60 mg/day, adjusted to 20 mg/day after 7 days) and control (atorvastatin 20 mg/day) groups. Combined aspirin and clopidogrel were used for antiplatelet therapy. Microemboli were monitored by transcranial Doppler on days 1 (pre-treatment), 3, and 7. Metalloproteinase-9 (MMP-9), high-sensitivity C-reactive protein (hs-CRP), and National Institutes of Health Stroke Scale (NIHSS) score were assessed on days 1 and 7. The modified Rankin scale (mRS) was used on day 90. The primary outcome was the proportion of patients with microemboli on day 3. **RESULTS:** There were 35 (58.3%) and 30 (52.6%) patients with microemboli in the intensive statin (n = 60) and control (n = 57) groups, respectively, on day 1 (p = 0.342). On day 3, there were significantly less microemboli in the intensive statin group (n = 9; 15.0%) compared with controls (n = 16; 28.1%; p = 0.002). No difference was observed in MMP-9 and hs-CRP levels on day 1, but on day 7, MMP-9 (median 79.3 vs. 95.9 mug/L; p = 0.004) and hs-CRP (median 2.01 vs. 3.60 mg/L; p = 0.020) levels were lower in the intensive statin group compared with controls. There were no differences in NIHSS scores on days 1 and 7. There was no difference in mRS on day 90. **CONCLUSION:** Intensive atorvastatin therapy in patients with acute ischemic stroke reduces the occurrence of microemboli and inflammation, with no overt adverse events.

[17] *Chan P, Shao L, Tomlinson B et al. An evaluation of pitavastatin for the treatment of hypercholesterolemia. Expert opinion on pharmacotherapy* 2018:1-11.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30482061>

ABSTRACT

INTRODUCTION: Statins are the first line of therapy to reduce low-density lipoprotein cholesterol (LDL-C) in order to decrease cardiovascular events. Pitavastatin is the latest statin to be introduced to the market. **Areas covered:** In this article, the authors review the efficacy, safety, and tolerability of pitavastatin. The authors also review a recent cardiovascular outcome study. **Expert opinion:** Pitavastatin produces dose-dependent reductions in LDL-C at lower doses than other statins. The maximum approved dose of 4 mg reduces LDL-C by about 40-49% in different patient groups and is equivalent to atorvastatin 20 mg in this effect. Pitavastatin undergoes minimal metabolism so drug-drug interactions are less likely than with many other statins, but it can interact with some drugs that inhibit drug transporters. Compared with other statins, it has been associated with greater increases in high-density lipoprotein cholesterol and it was found to be less likely to cause new onset diabetes. In a recent study in Japanese patients with stable coronary artery disease, pitavastatin 4 mg was more effective than pitavastatin 1 mg in reducing cardiovascular events. Therefore, the highest dose may be preferred in high-risk patients.

[18] *Hedrington MS, Davis SN. Oral semaglutide for the treatment of type 2 diabetes. Expert opinion on pharmacotherapy* 2018:1-9.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30499733>

ABSTRACT

INTRODUCTION: Glucagon-like peptide-1 (GLP-1) receptor agonists are highly potent antihyperglycemic drugs that impose low risk of hypoglycemia and also result in body weight

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reduction. Currently, all approved members of the class require administration by injection. Areas covered: This manuscript reviews oral semaglutide-an experimental GLP-1 receptor agonist in phase-3 clinical development. Available pharmacological and clinical data of the drug are reviewed, and important end-points described. Expert opinion: Oral peptide delivery has become possible with the discovery of absorption enhancers. The clinical development program of once-daily oral semaglutide has shown superiority in reducing glycosylated hemoglobin and body weight in comparison with placebo and active comparators (sitagliptin, liraglutide, and empagliflozin). Safety and tolerability of oral semaglutide is in line with injectable members of the class. Delayed gastric emptying, local increase in pH, and enhanced absorption do not seem to affect the exposure of a number of other oral drugs that have been tested (metformin, digoxin, oral contraceptive ethinylestradiol/levonorgestrel, lisinopril, warfarin, furosemide and rosuvastatin). Clinical questions for further investigation include the effectiveness and safety of oral semaglutide in cardiovascular indications.

[19] Guo T, Liu Q, Hou P et al. **Stilbenoids and cannabinoids from the leaves of *Cannabis sativa f. sativa* with potential reverse cholesterol transport activity.** *Food & function* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30500001>

ABSTRACT

Three new stilbenoids (1-3) and 16 known stilbenoids (4-6) and cannabinoids (7-19) were isolated from the leaves of hemp (*Cannabis sativa* L.). The structures of the three new compounds were identified as alpha, alpha'-dihydro-3',4,5'-trihydroxy-4'-methoxy-3-isopentenylstilbene (HM1), alpha, alpha'-dihydro-3,4,5-trihydroxy-4-methoxy-2,6-diisopentenylstilbene (HM2), and alpha, alpha'-dihydro-3',4,5'-trihydroxy-4'-methoxy-2',3-diisopentenylstilbene (HM3) by 1D and 2D NMR spectroscopy, LC-MS, and HRESIMS. The known alpha, alpha'-dihydro-3,4,5-trihydroxy-4,5'-diisopentenylstilbene (5) and combretastatin B-2 (6) were isolated for the first time from *C. sativa f. sativa*. These isolated compounds exhibited cytotoxic effects on human cancer cells via inhibiting the proliferation of cancer cells and inducing cell death. Among them, compounds 4, 5, 10, 12, 13, 15, and 19 displayed broad-spectrum cytotoxicity, and 1, 7, and 11 displayed selectivity in inhibition efficiency on MCF-7 and A549 cells, which suppressed the proliferation of cancer cells significantly by inducing cell death. The effects of compounds 1-3 on improving reverse cholesterol transport (RCT) were evaluated by isotope-tracing and western blotting. Results showed that the three stilbenoids showed a cytotoxicity above 1.0 mg L⁻¹, especially that of HM3. They could improve [3H]-cholesterol efflux from Raw 264.7 macrophages to high density lipoproteins by enhancing the protein expression of ABCG1 and SR-B1, and HM1 and HM2 showed a significant difference compared with fenofibrate at 1.0 mg L⁻¹. The three stilbenoids could also significantly improve the protein expression of ABCA1. Further study on HepG2 cells indicated that they improve the protein expression of LDLR, SR-B1 and CYP7A1, especially that of HM1 and HM3. However, they showed no significant effect on PCSK9. The above results indicated that these stilbenoids may elevate the transfer of cholesterol to hepatocytes by improving the protein expression of SR-B1 and LDLR, and the synthesis of bile acid by increasing the protein expression of CYP7A1. In conclusion, HM1 showed lower cytotoxicity and higher activity in improving the RCT-related protein expression. Our study suggests that it may be explored as a novel lipid-lowering drug and as a beneficial ingredient in health functional foods and pharmaceuticals.

[20] Baik SY, Kim H, Yang SJ et al. **Long-term effects of various types of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors on changes in glomerular filtration rate in Korea.** *Frontiers of medicine* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30483915>

ABSTRACT

Few long-term follow-up studies have compared the changes in renal function according to the type of statin used in Korea. We compared the long-term effects of statin intensity and type on the changes in the glomerular filtration rate (GFR). We extracted data of patients who took statin for the first time. We analyzed whether or not different statins affect the changes in GFR at 3 months after baseline and 4 years after. We included 3678 patients and analyzed the changes in GFR. The GFR decreased by 3.2%±0.4% on average 4 years after the first statin prescription, indicating statistically significant deterioration (from 83.5±0.4 mL/min/1.73 m² to 79.9±0.4 mL/min/1.73 m², P < 0.001). When comparing the GFR among different statins, significant differences were observed between atorvastatin and fluvastatin (-5.3%±0.7% vs. 1.2%±2.2%, P < 0.05) and between atorvastatin and simvastatin (-5.3%±0.7% vs. -0.7%±0.8%, P < 0.05). In pitavastatin (odds ratio [OR]= 0.64, 95% confidence interval [CI]= 0.46-0.87, P < 0.005) and simvastatin (OR = 0.69, 95% CI = 0.53-0.91, P < 0.008), the GFR rate that decreased by < 60 mL/min/1.73 m² was significantly lower than that of atorvastatin. Regarding long-term statin intake, GFR changed with the type of statin. This work is the first in Korea to compare each statin in terms of changes in the GFR after the statin prescription.

[21] Roth EM. **Alirocumab for low-density lipoprotein cholesterol lowering.** *Future cardiology* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30499328>

ABSTRACT

Ischemic heart disease and stroke are the leading causes of death in the world currently. Both of these conditions are primarily caused by atherosclerosis, the underlying pathophysiology of which is the deposition of lipid, specifically low-density lipoprotein cholesterol (LDL-C) within the arterial bed. Proprotein convertase subtilisin kexin type 9 (PCSK9), is a proteolytic enzyme, which indirectly increases LDL-C levels by causing the destruction of LDL receptors, the main way that humans regulate their serum LDL-C levels. Inhibitors of PCSK9 in conjunction with statins have allowed achievement of very low LDL-C levels. This review will provide an in-depth efficacy and safety review of alirocumab, a monoclonal antibody inhibitor of PCSK9, including the ODYSSEY OUTCOMES trial.

[22] Zhang L, Zhang S, Yu Y et al. **Efficacy and safety of rosuvastatin vs. atorvastatin in lowering LDL cholesterol : A meta-analysis of trials with East Asian populations.** *Herz* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30483816>

ABSTRACT

BACKGROUND: The VOYAGER meta-analysis reported on the low-density lipoprotein cholesterol (LDL-C)-lowering effect of commonly used statins in Caucasian subjects. As there is limited literature available on the efficacy of statins in Asian populations, the current meta-analysis compared the effects of rosuvastatin and atorvastatin on LDL-C levels in an East Asian

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population. METHODS: The MEDLINE, PubMed, Embase, Cochrane Library, and Web of Science databases were searched for randomized controlled trials comparing lipid-lowering effects of rosuvastatin and atorvastatin in an East Asian population. Data on the study design, participant characteristics, and outcomes were extracted. Odds ratios (OR), weighted mean differences (WMD), or standardized mean differences were calculated using the random-effects model. RESULTS: The meta-analysis comprised 16 randomized controlled trials with 5930 participants. Compared with atorvastatin, patients treated with rosuvastatin had a significant reduction in LDL-C: WMD= -7.15mg/dl (95% confidence intervals [CI]: -10.71--3.60) mg/dl, $p < 0.0001$. Meta-regression analyses revealed no significant association between the superior benefits of rosuvastatin and other variables including age, sex, baseline LDL-C level, and follow-up duration. Additionally, the rosuvastatin group of patients, who were treated with half the dose of atorvastatin, achieved a significantly greater reduction in LDL-C levels (WMD= -3.57; 95% CI: -5.40--1.74mg/dl, $p < 0.001$). Both rosuvastatin and atorvastatin were well tolerated, with similar incidences of adverse events. CONCLUSION: Similar to the VOYAGER meta-analysis, which reported a greater efficacy of rosuvastatin in comparison with atorvastatin and simvastatin in Caucasian patients, we found that the efficacy of rosuvastatin was superior to atorvastatin in East Asian patients with hypercholesterolemia.

[23] *Hajihassani Biouki M, Mobedi H, Karkhaneh A, Daliri Joupari M. Development of a simvastatin loaded injectable porous scaffold in situ formed by phase inversion method for bone tissue regeneration. The International journal of artificial organs 2018;391398818806161. PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30482084>*

ABSTRACT

INTRODUCTION:: The use of injectable scaffolds as a minimally invasive method is a good choice in tissue engineering applications. A critical parameter for the tissue engineering scaffolds is a suitable morphology with interconnected pores. We present the development of a simvastatin loaded scaffold that forms in situ and provides the porous structure with interconnected pores. METHODS:: The formulation of these scaffolds includes a polymeric solution of poly lactic-co-glycolic acid (25 wt%) in N-methyl-2-pyrrolidone containing 6 wt% deionized water and porogen (mannitol, four times the weight of the polymer). We have grafted simvastatin to poly lactic-co-glycolic acid by the esterification reactions. Simvastatin or simvastatin-grafted poly lactic-co-glycolic acid in different levels was added to polymer solution and finally the solution was injected into phosphate buffered saline. The simvastatin-grafted poly lactic-co-glycolic acid was characterized by attenuated total reflection Fourier-transform infra-red and (1)H-nuclear magnetic resonance spectroscopy. The morphology, porosity, and biocompatibility of the scaffolds were evaluated. The in vitro simvastatin release from the various formulations was studied. Osteogenic differentiation of the adipose-derived stem cells was investigated using alkaline phosphatase activity assay and cell mineralization was evaluated using Alizarin red staining. RESULTS:: The morphology results showed the resultant scaffold was porous with the interconnected pores. The scaffolds presented 91% porosity. Non-toxic doses of simvastatin in the scaffolds were determined by methyl-thiazolyl diphenyl-tetrazolium bromide assay. The released simvastatin from the scaffolds continues over 80 days. Alkaline phosphatase activity and Alizarin red results indicated that cell osteogenic differentiation is promoted. CONCLUSION:: The results demonstrated that release of simvastatin from the

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injectable scaffolds can have positive effects on osteogenic differentiation of the adipose-derived stem cells.

[24] *Bocate KP, Reis GF, de Souza PC et al. Antifungal activity of silver nanoparticles and simvastatin against toxigenic species of Aspergillus. International journal of food microbiology* 2018; 291:79-86.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30476736>

ABSTRACT

Aspergillus spp. are ubiquitous fungi that grow on stored grains. Some species produce toxins that can harm human and animal health, leading to hepato- and nephrotoxicity, immunosuppression and carcinogenicity. Major fungicides used to prevent fungal growth may be toxic to humans and their repeated use over time increases levels of resistance by microorganisms. Nanotechnology is an emerging field that allows use of antimicrobial compounds in a more efficient manner. In this study, was evaluated the antifungal activity of biogenic silver nanoparticles (AgNPs, synthesized by fungi) and simvastatin (SIM, a semi-synthetic drug), alone and in combination against three toxigenic species belonging to the genera *Aspergillus* section Flavi (*Aspergillus flavus*, *Aspergillus nomius* and *Aspergillus parasiticus*) and two of section Circumdati (*Aspergillus ochraceus* and *Aspergillus melleus*). SIM exhibited a MIC50 of 78µg/mL against species of Section Flavi and a MIC50 of 19.5µg/mL against species of Section Circumdati. The MIC50 of AgNPs against *Aspergillus flavus*, *Aspergillus nomius* and *Aspergillus parasiticus* was 8µg/mL, while the MIC50 was 4µg/mL against *Aspergillus melleus* and *Aspergillus ochraceus*. Checkerboard assay showed that these compounds, used alone and in combination, have synergistic and additive effects against toxicogenic species of *Aspergillus*. Analysis by SEM gives an idea of the effect of SIM and AgNPs alone and in combination on spore germination and vegetative growth. Ultrastructural analysis revealed that spore germination was prevented, or aberrant hyphae were formed with multilateral branches upon treatment with SIM and AgNPs. These results reveal potential benefits of using combination of AgNPs and SIM to control fungal growth.

[25] *Montastier E, Beuzelin D, Martins F et al. Niacin induces miR-502-3p expression which impairs insulin sensitivity in human adipocytes. International journal of obesity (2005)* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30482933>

ABSTRACT

MicroRNAs have been involved in insulin resistance (IR). As the mechanism whereby niacin, an anti-dyslipidemic agent, leads to IR remains elusive, we sought to identify differentially expressed microRNAs in adipose tissue (AT) of individuals receiving niacin and to explore the link between microRNAs, niacin and IR in human adipocytes. In a double-blind controlled study, 22 obese men received extended-release niacin or placebo over 8 weeks. Bioclinical data and subcutaneous AT biopsies were obtained before and after treatment. AT microRNA expression profiles were determined using RTqPCR for 758 human-specific microRNAs. hMADS adipocytes were treated with niacin, or acipimox (a niacin-like drug without effect on IR), or transfected with miR-502-3p. Glucose uptake and Western blotting were performed. In obese men, insulin sensitivity decreased after niacin treatment. In AT, the expression of 6 microRNAs including miR-502-3p was up-regulated. Treatment of hMADS adipocytes with niacin specifically

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increased miR-502-3p expression. Acipimox had no effect. Overexpression of miR-502-3p in adipocytes led to reduced insulin-induced glucose uptake and lower insulin-stimulated AKT phosphorylation. Long term niacin treatment altered microRNA expression levels in human AT. Increased miR-502-3p expression may play a role in the mediation of IR due to niacin in adipocytes. The study is registered in Clinical Trials NCT01083329 and EudraCT 2009-012124-85.

[26] *Kithcart AP, Beckman JA. ACC/AHA Versus ESC Guidelines for Diagnosis and Management of Peripheral Artery Disease: JACC Guideline Comparison. Journal of the American College of Cardiology 2018; 72:2789-2801.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30497565>

ABSTRACT

Peripheral artery disease is a common yet underdiagnosed cause of morbidity worldwide. Significant recent advances in management have resulted in new guideline creation for the diagnosis and management of peripheral artery disease in the United States and Europe. Here, we analyze each set of guidelines with special attention to those areas where the 2 groups disagree. Both groups emphasize the importance of risk factor reduction, including smoking cessation, lipid lowering, blood pressure management, and glucose control. The U.S. guidelines place additional attention on lifestyle factors, including regular physical activity and supervised exercise. The European guidelines offer a number of recommendations for revascularization in patients with limb-threatening ischemia. Both agree that more evidence is needed to understand which patients are at highest risk for tissue loss. A consistent charge to each committee fostering a similar approach to available data and more randomized studies would align recommendations across both organizations.

[27] *Fang D, Jin Q, Jin Z et al. Folate-Modified Liposomes Loaded with Telmisartan Enhance Anti-Atherosclerotic Potency for Advanced Atherosclerosis in ApoE(-/-) Mice. Journal of biomedical nanotechnology 2019; 15:42-61.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30480514>

ABSTRACT

For the effective inhibition of atherosclerotic plaque rupture, there is an urgent need to develop a carrier which can specifically deliver the therapeutic agents to atherosclerotic lesions. Since the representative hallmark of plaques in advanced atherosclerosis is the large number of macrophages which highly upregulate folate receptor beta (FR-beta), we herein investigated the potential of folate-modified liposomes (FA-P-LP) as the carrier for active targeting of atherosclerotic plaques. In vitro cellular uptake tests, FA-P-LP exhibited an enhanced uptake in activated RAW264.7 macrophages with high expression of FR-beta, whereas this enhanced effect was dramatically diminished when the cells were pretreated with excess amount of free folate, indicating that FA-P-LP were mainly taken up by the receptor-mediated endocytosis. From the in vivo distribution assay, it was confirmly demonstrated that FA-P-LP significantly accumulated in atherosclerotic lesions and were co-localized with macrophages within plaques. Thereafter, we utilized the FA-P-LP to deliver an angiotensin receptor blocker (ARB), telmisartan (Tel), to macrophages in atherosclerotic plaques and evaluated their therapeutic effects on plaque destabilization. After 12 weeks treatment in ApoE(-/-) mice with established atherosclerosis, FA-P-LP/Tel exerted a marked improvement in key advanced plaque properties

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without affecting the plasma lipid level and blood pressure. These beneficial effects include the regression of atherosclerotic plaques possibly attributing to the enhanced cellular cholesterol efflux and reduced macrophage infiltration, an increase in the protective collagen layer overlying lesions resulting from suppression of collagenase activity and decrease in matrix 2/9 (MMP 2/9) expression, suppression of oxidative stress, and a reduction in plaque necrosis and calcification. Thus, administration of Tel in a targeted liposome could stabilize the advanced atherosclerotic lesions independent of lipid lowering and blood pressure decrease. In conclusion, FA-P-LP could effectively home to the atherosclerotic lesion through the active targeting mechanism after systemic administration, indicating their high potential as the carrier for atherosclerosis therapy. Together, the FA-P-LP/Tel would be considered as a promising nanotherapeutic approach to prevent plaque rupture, providing an alternative regimen for clinical treatment of advanced atherosclerosis.

[28] *Amin SA, Adhikari N, Gayen S, Jha T. Reliable structural information for rational design of benzoxazole type potential cholesteryl ester transfer protein (CETP) inhibitors through multiple validated modelling techniques. Journal of biomolecular structure & dynamics 2018:1-17.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30488780>

ABSTRACT

The drug design and discovery of lipid modulators is very demanding as no new molecule has entered into the market in the last 35 years. Cholesteryl ester transfer protein (CETP) is a promising target as lipid modulators. Inhibition of the CETP enzyme reduces the risk of cardiovascular events. The first CETP inhibitor torcetrapib and related drug candidates failed in the clinical trial due to the off target effects leading to high toxicity. Thus, newer ETP inhibitors have now paramount importance to accelerate the drug discovery efforts in the field of cardiovascular disease (CVD). In the present study, 140 benzoxazole compounds were studied by using different chemometric techniques for example pharmacophore mapping, molecular docking, 3D QSAR-CoMFA, Topomer CoMFA and Bayesian classification, in order to generate complete and reliable information regarding the structural requirements for the CETP inhibition. The best pharmacophore hypothesis was statistically significant (regression coefficient of 0.957 and a lower root mean square of 0.897). Molecular docking study revealed that cyano substituted compounds form hydrogen bond with targeted macromolecule. The 3D-QSAR CoMFA model also produced a LOO-cross validated Q(2) of 0.527, an R(2) of 0.853 and an R(2)Pred of 0.603. Similarly, two topomer CoMFA models were also statistically significant and reliable in terms of their Q(2), R(2) and R(2)Pred values. The Bayesian classification study also provided the excellent ROC values of 0.919 and 0.939 for training and test sets respectively. Overall, this study may help in the rational design of newer benzoxazole type compounds with higher CETP inhibition.

[29] *Crump B. A closer look at an ezetimibe discussion. The Journal of family practice 2018; 67:675-676.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30481250>

ABSTRACT

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[30] *Ridker PM. Anti-Inflammatory Therapy for Atherosclerosis: Interpreting Divergent Results from the CANTOS and CIRT Clinical Trials. Journal of internal medicine* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30472762>

ABSTRACT

Over the past 18 months, two multi-national clinical trials specifically designed to test the inflammation hypothesis of atherothrombosis have been presented. First, the 10,061 patient Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) proved that specific targeting of interleukin-1beta can significantly reduce cardiovascular event rates in the absence of lipid or blood pressure lowering. In CANTOS, canakinumab given at doses of either 150 or 300 mg SC once every three months lowered the inflammatory biomarkers interleukin-6 and C-reactive protein (hsCRP) by 35 to 40 percent when compared to placebo, effects that led to a 17 percent reduction in rates of recurrent heart attack, stroke, urgent need for revascularization, or cardiovascular death (P<0.001). This article is protected by copyright. All rights reserved.

[31] *Castro AR, Silva SO, Soares SC. The Use of High Sensitivity C-Reactive Protein in Cardiovascular Disease Detection. Journal of pharmacy & pharmaceutical sciences : a publication of the Canadian Society for Pharmaceutical Sciences, Societe canadienne des sciences pharmaceutiques* 2018; 21:496-503.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30496036>

ABSTRACT

Cardiovascular diseases (CVDs) are responsible for a high mortality rate worldwide. One of the most common causes of CVDs is vascular inflammation associated to atherosclerosis. Inflammatory biomarkers are used to assist the detection of CVDs and monitor their evaluation, prognosis and therapy implementation. C-reactive protein (CRP) is an acute phase protein produced after stimulation by pro-inflammatory cytokines. CRP is a biomarker of the inflammatory reaction and an important mediator of atherosclerosis. Given it actively contributes to the development of the atherosclerotic plaque, instability and subsequent clot formation it is also considered a CVD risk factor. Since 2010, the plasma concentration of hsCRP (high sensitivity CRP) has been used as a biomarker for disease prognosis in patients with intermediate risk for CVDs. It could be useful to establish a high concentration limit of hsCRP that can be used by clinicians for diagnosis of acute myocardial infarction, cardio embolic or ischemic stroke, and hypertrophic cardiomyopathy. The end cost/effectiveness of hsCRP screening is still an area of controversy but it is a priority to make the medical community aware of the positive relation between high hsCRP and CVDs to improve median survival and life quality of the patients.

[32] *Capoulade R, Yeang C, Chan KL et al. Association of Mild to Moderate Aortic Valve Stenosis Progression With Higher Lipoprotein(a) and Oxidized Phospholipid Levels: Secondary Analysis of a Randomized Clinical Trial. JAMA cardiology* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30476957>

ABSTRACT

Importance: Several studies have reported an association of levels of lipoprotein(a) (Lp[a]) and the content of oxidized phospholipids on apolipoprotein B (OxPL-apoB) and apolipoprotein(a) (OxPL-apo[a]) with faster calcific aortic valve stenosis (CAVS) progression. However, whether

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this association is threshold or linear remains unclear. Objective: To determine whether the plasma levels of Lp(a), OxPL-apoB, and OxPL-apo(a) have a linear association with a faster rate of CAVS progression. Design, Setting, and Participants: This secondary analysis of a randomized clinical trial tested the association of baseline plasma levels of Lp(a), OxPL-apoB, and OxPL-apo(a) with the rate of CAVS progression. Participants were included from the ASTRONOMER (Effects of Rosuvastatin on Aortic Stenosis Progression) trial, a multicenter study conducted in 23 Canadian sites designed to test the effect of statin therapy (median follow-up, 3.5 years [interquartile range, 2.9-4.5 years]). Patients with mild to moderate CAVS defined by peak aortic jet velocity ranging from 2.5 to 4.0 m/s were recruited; those with peak aortic jet velocity of less than 2.5 m/s or with an indication for statin therapy were excluded. Data were collected from January 1, 2002, through December 31, 2005, and underwent ad hoc analysis from April 1 through September 1, 2018. Interventions: After the randomization process, patients were followed up by means of echocardiography for 3 to 5 years. Main Outcomes and Measures: Progression rate of CAVS as assessed by annualized progression of peak aortic jet velocity. Results: In this cohort of 220 patients (60.0% male; mean [SD] age, 58 [13] years), a linear association was found between plasma levels of Lp(a) (odds ratio [OR] per 10-mg/dL increase, 1.10; 95% CI, 1.03-1.19; P = .006), OxPL-apoB (OR per 1-nM increase, 1.06; 95% CI, 1.01-1.12; P = .02), and OxPL-apo(a) (OR per 10-nM increase, 1.16; 95% CI, 1.05-1.27; P = .002) and faster CAVS progression, which is marked in younger patients (OR for Lp[a] level per 10-mg/dL increase, 1.19 [95% CI, 1.07-1.33; P = .002]; OR for OxPL-apoB level per 1-nM increase, 1.06 [95% CI, 1.02-1.17; P = .01]; and OR for OxPL-apo[a] level per 10-nM increase, 1.26 [95% CI, 1.10-1.45; P = .001]) and remained statistically significant after comprehensive multivariable adjustment (beta coefficient, ≥ 0.25 ; SE, ≤ 0.004 [P $\leq .005$]; OR, ≥ 1.10 [P $\leq .007$]). Conclusions and Relevance: This study demonstrates that the association of Lp(a) levels and its content in OxPL with faster CAVS progression is linear, reinforcing the concept that Lp(a) levels should be measured in patients with mild to moderate CAVS to enhance management and risk stratification. Trial Registration: ClinicalTrials.gov Identifier: NCT00800800.

[33] Yan Z, Miao X, Zhang B, Xie J. **p53 as a double-edged sword in the progression of non-alcoholic fatty liver disease.** *Life sciences* 2018; 215:64-72.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30473026>

ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) derives from the accumulation of hepatic lipids, which leads to liver steatosis and then triggers non-alcoholic steatohepatitis, sometimes worsening to hepatic fibrosis, cirrhosis, and hepatocellular carcinoma. Although the molecular mechanisms of NAFLD have been intensively investigated, its pathogenesis remains poorly understood and needs to be clarified. Tumor-suppressor factor p53 has a crucial role in many signaling pathways that induce apoptosis and has become an emerging focus for liver disease research. Recent studies have revealed that p53 is linked to the development of NAFLD and that the regulation of p53 has therapeutic potential. However, the association between p53 and NAFLD remains controversial. Several reports have suggested that activated p53 plays an essential role in the pathogenesis of NAFLD, whereas others have indicated that suppression of p53 activation aggravates liver steatosis. Here, we review the relevant evidence suggesting that these two contrasting processes indicate a dual role of p53 in NAFLD progression and propose that the

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extent of NAFLD may be key to explaining the contradictory findings. In this review, the crosstalk among p53, lipid metabolism, insulin resistance, inflammation and oxidative stress in NAFLD is discussed, and we suggest that a better understanding of p53 would present a promising potential new strategy for NAFLD prevention and treatment.

[34] *Dettlaff-Pokora A, Sucajtyś-Szulc E, Sledziński T. Up-regulation of PCSK9 gene expression and diminished level of LDL-receptor in rat liver as a potential cause of post-lipectomy hypercholesterolemia. Molecular and cellular biochemistry* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30483910>

ABSTRACT

Studies designed to examine effects of fat mass reduction (including lipodystrophy and lipectomy) on human serum total and LDL-cholesterol concentrations are inconsistent. The purpose of this study was to examine effect of partial lipectomy in rats (as an experimental model of fat mass reduction in humans) on (1) circulating total cholesterol, LDL-cholesterol + VLDL-cholesterol and HDL-cholesterol concentrations, and (2) factors which may affect serum cholesterol concentrations such as: (a) liver LDL-receptor level, (b) expression of liver PCSK9 and (c) circulating PCSK9 concentration. Reduction of rat adipose tissue mass resulted in an increase in circulating total and LDL + VLDL-cholesterol concentrations, which was associated with (a) decrease in liver LDL-R level, (b) increase in liver PCSK9 expression, and (c) increase in circulating PCSK9 concentration as compared with sham controls. These changes were accompanied by elevated liver HNF1alpha (and HNF4alpha) mRNA levels. Silencing HNF1alpha in HepG2 cells by siRNA led to decrease in PCSK9 mRNA levels. This suggests that overexpression of HNF1alpha gene in liver of lipectomized rats can lead to overproduction of PCSK9. In conclusion, up-regulation of PCSK9, due to overexpression of HNF1alpha gene in liver of lipectomized rats and subsequently increase in circulating PCSK9 concentration lead to decrease in liver LDL-R level. This may contribute, at least in part, to an increase in the concentration of circulating cholesterol in rats with reduced fat mass. These findings provide a possible explanation for the molecular mechanism of hypercholesterolemia observed sometimes after reduction of fat mass in human.

[35] *Geng J, Xu H, Yu X et al. Rosuvastatin protects against oxidized lowdensity lipoproteininduced endothelial cell injury of atherosclerosis in vitro. Molecular medicine reports* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30483737>

ABSTRACT

Atherosclerosisinduced cardiovascular diseases (CVDs) are accompanied by substantial morbidity and mortality. The loss and injury of endothelial cells is the primary cause of atherosclerosis. Rosuvastatin is an alternative agent used to reduce the risk of cardiovascular disease. Subsequently, the present study aimed to investigate the protective effects of rosuvastatin on oxidizedlowdensity lipoprotein (oxLDL)induced human umbilical vein endothelial cell (HUVEC) injury. The viability of oxLDLcultured HUVECs with or without rosuvastatin (0.01, 0.1 and 1 micromol/l) pretreatment, and pretreatment at different time points (3, 6, 12 and 24 h) was determined using an MTT assay. Morphological changes and the extent of apoptosis were detected; the antioxidase activity, including superoxide dismutase

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(SOD) and catalase (CAT), was examined, and the contents of malondialdehyde (MDA) and nitric oxide (NO) were measured. The phosphorylation levels of endothelial nitric oxide synthase (eNOS), protein kinase B (Akt) and phosphoinositide 3 kinase (PI3K) were detected using western blot analysis. The results demonstrated that pretreatment with 0.011 micromol/l rosuvastatin decreased cell apoptosis caused by oxLDL. Notably, pretreatment with 1 micromol/l rosuvastatin for >12 h increased cell viability. Additionally, DAPI staining revealed that rosuvastatin inhibited HUVEC apoptosis. Rosuvastatin treatment also resulted in increased SOD and CAT activities and decreased MDA content in oxLDL-stimulated HUVECs. Furthermore, pretreatment with 0.011 micromol/l rosuvastatin significantly increased the NO content compared with HUVECs treated with oxLDL alone. Western blot analyses demonstrated that rosuvastatin upregulated the phosphorylation of eNOS, Akt and PI3K. These findings indicated that rosuvastatin could protect HUVECs against oxLDL-induced injury through its antioxidant effect and its ability to upregulate the expression of vascular endotheliocyte-protecting factors.

[36] *Burnett JR, Hooper AJ. PCSK9 - A Journey to Cardiovascular Outcomes. The New England journal of medicine* 2018; 379:2161-2162.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30485782>

ABSTRACT

[37] *Fernandez-Ruiz I. Targeting PCSK9 to reduce residual risk in ACS. Nature reviews. Cardiology* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30478399>

ABSTRACT

[38] *Parihar SP, Guler R, Brombacher F. Statins: a viable candidate for host-directed therapy against infectious diseases. Nature reviews. Immunology* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30487528>

ABSTRACT

Statins were first identified over 40 years ago as lipid-lowering drugs and have been remarkably effective in treating cardiovascular diseases. As research advanced, the protective effects of statins were additionally attributed to their anti-inflammatory, antioxidative, anti-thrombotic and immunomodulatory functions rather than lipid-lowering abilities alone. By promoting host defence mechanisms and inhibiting pathological inflammation, statins increase survival in human infectious diseases. At the cellular level, statins inhibit the intermediates of the host mevalonate pathway, thus compromising the immune evasion strategies of pathogens and their survival. Here, we discuss the potential use of statins as an inexpensive and practical alternative or adjunctive host-directed therapy for infectious diseases caused by intracellular pathogens, such as viruses, protozoa, fungi and bacteria.

[39] *Maas R, Mieth M, Titze SI et al. Drugs linked to plasma homoarginine in chronic kidney disease patients-a cross-sectional analysis of the German Chronic Kidney Disease cohort. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30476224>

ABSTRACT

Background: Elevated plasma concentrations of symmetric and asymmetric dimethylarginine (SDMA and ADMA, respectively) and a lower plasma concentration of the structurally related homoarginine are commonly observed in patients with chronic kidney disease (CKD) and independently predict total mortality as well as progression of renal disease. We aimed to identify drugs that may alter this adverse metabolite pattern in a favourable fashion. Methods: Plasma ADMA, SDMA, homoarginine and l-arginine were determined by liquid chromatography-tandem mass spectrometry in 4756 CKD patients ages 18-74 years with an estimated glomerular filtration rate (eGFR) of 30-60 mL/min/1.73 m² or an eGFR >60 mL/min/1.73 m² and overt proteinuria who were enrolled in the German Chronic Kidney Disease (GCKD) study. Associations between laboratory, clinical and medication data were assessed. Results: Intake of several commonly used drugs was independently associated with plasma concentrations of homoarginine and/or related metabolites. Among these, the peroxisome proliferator-activated receptor alpha (PPAR-alpha) agonist fenofibrate was associated with the most profound differences in ADMA, SDMA and homoarginine plasma concentrations: 66 patients taking fenofibrate had a multivariable adjusted odds ratio (OR) of 5.83 [95% confidence interval (CI) 2.82-12.03, P < 0.001] to have a plasma homoarginine concentration above the median. The median homoarginine plasma concentration in patients taking fenofibrate was 2.30 micromol/L versus 1.55 in patients not taking the drug (P < 0.001). In addition, fibrates were significantly associated with lower plasma SDMA and higher l-arginine concentrations. In contrast, glucocorticoids were associated with lower plasma homoarginine, with adjusted ORs of 0.52 (95% CI 0.40-0.67, P < 0.001) and 0.53 (95% CI 0.31-0.90, P = 0.018) for prednisolone and methylprednisolone, respectively. Conclusions: In a large cohort of CKD patients, intake of fenofibrate and glucocorticoids were independently associated with higher and lower plasma homoarginine concentrations, respectively. Effects on plasma homoarginine and methylarginines warrant further investigation as potential mechanisms mediating beneficial or adverse drug effects.

[40] *Polster SP, Stadnik A, Akers AL et al. Atorvastatin Treatment of Cavernous Angiomas with Symptomatic Hemorrhage Exploratory Proof of Concept (AT CASH EPOC) Trial. Neurosurgery 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30476251>

ABSTRACT

BACKGROUND: More than a million Americans harbor a cerebral cavernous angioma (CA), and those who suffer a prior symptomatic hemorrhage have an exceptionally high rebleeding risk. Preclinical studies show that atorvastatin blunts CA lesion development and hemorrhage through inhibiting RhoA kinase (ROCK), suggesting it may confer a therapeutic benefit.

OBJECTIVE: To evaluate whether atorvastatin produces a difference compared to placebo in lesional iron deposition as assessed by quantitative susceptibility mapping (QSM) on magnetic resonance imaging in CAs that have demonstrated a symptomatic hemorrhage in the prior year. Secondary aims shall assess effects on vascular permeability, ROCK activity in peripheral leukocytes, signal effects on clinical outcomes, adverse events, and prespecified subgroups.

METHODS: The phase I/IIa placebo-controlled, double-blinded, single-site clinical trial aims to enroll 80 subjects randomized 1-1 to atorvastatin (starting dose 80 mg PO daily) or placebo.

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Dosing shall continue for 24-mo or until reaching a safety endpoint. EXPECTED OUTCOMES: The trial is powered to detect an absolute difference of 20% in the mean percent change in lesional QSM per year (2-tailed, power 0.9, alpha 0.05). A decrease in QSM change would be a signal of potential benefit, and an increase would signal a safety concern with the drug. DISCUSSION: With firm mechanistic rationale, rigorous preclinical discoveries, and biomarker validations, the trial shall explore a proof of concept effect of a widely used repurposed drug in stabilizing CAs after a symptomatic hemorrhage. This will be the first clinical trial of a drug aimed at altering rebleeding in CA.

[41] Schob M, Muller P, Gerth Y et al. **[Diagnosis and Treatment of Familial Hypercholesterolemia]**. *Praxis* 2018; 107:1345-1353.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30482120>

ABSTRACT

Diagnosis and Treatment of Familial Hypercholesterolemia Abstract. Familial hypercholesterolemia secondary to heterozygous mutations in the LDL receptor, Apolipoprotein B or PCSK9 gene is characterized by 2- to 3-fold elevated LDL cholesterol levels, premature atherosclerosis and extravascular cholesterol deposits (tendon xanthomata, corneal arcus). The same phenotype may occur if a person carries several LDL cholesterol rising polymorphisms (polygenic FH). Primary prevention with statins has been shown to dramatically reduce the cardiovascular burden in patients with the disease. However, it is estimated that less than 10 % of affected subjects in Switzerland have received the diagnosis, and undertreatment is frequent. Thus, clinical cardiovascular events are still the first manifestation of the disease in many cases. A correct diagnosis in index patients and cascade screening of families are mandatory to identify and treat patients before they suffer the sequelae of untreated severe hypercholesterolemia. In patients with clinical cardiovascular disease combination lipid lowering treatment with potent statins, ezetimibe and the newly available PCSK9 inhibitors will successfully lower LDL cholesterol to normal or even target levels.

[42] Riaz S, John S. Cholestyramine Resin. In: StatPearls. Treasure Island (FL): StatPearls Publishing

StatPearls Publishing LLC.; 2018.

[43] Dolladille C, Humbert X, Faucon M et al. **Association between venous thromboembolism events and fibrates: A comparative study**. *Therapie* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30482666>

ABSTRACT

AIM: Previous studies highlighted a significant association between fibrates and venous thromboembolism (VTE) events in dyslipidemia diabetic patients. Studies in non-diabetic patients are divergent. The present study investigated the association between VTE events and fibrates in diabetic and non-diabetic patients. METHODS: Two approaches were used: (1) a disproportionality analysis using the World health organization pharmacovigilance database VigiBase((R)) was used to evaluate the reporting odds-ratio (ROR) of fibrates for VTE events. Clinical and demographic characterizations of patients with fibrates-related VTE reports are described; (2) a case control-study was performed using the Caen university hospital medical information database between January 2008 and December 2012. Cases were dyslipidemia

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patients who were hospitalized for VTE without an evident provoking factor. Up to four controls per case were selected in dyslipidemia patients hospitalized for a non-VTE event. Controls were matched to cases by age, gender, date of hospitalization, diabetes, chronic kidney disease and hospitalization department. A multivariate conditional logistic regression was performed. RESULTS: Disproportionality analysis: a total of 946 notifications were identified in VigiBase((R)) (32.9% of diabetic patients). Fibrates were significantly associated with an increased report of VTE (ROR 1.14, CI 1.07-1.22). Case-control study: a total of 163 cases (21.5% of diabetic patients) and 514 matched controls were recruited. Fibrates were significantly associated with a higher risk of VTE events that required hospitalization in multivariate analysis (odds-ratio (OR) 3.67, CI 1.82-7.37, P=0.0003). The association was only significant for fenofibrate in both approaches. CONCLUSION: Fenofibrate was associated with a higher incidence of VTE events in diabetic and non-diabetic patients.

[44] Song ZC, Chen L, Zhang D et al. [Rosuvastatin protects acute myocardial infarction rats through autophagy regulation via AMPK signaling]. *Zhonghua yi xue za zhi* 2018; 98:3536-3541.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30481906>

ABSTRACT

Objective: To investigate the effects of rosuvastatin (RSV) on autophagy and apoptosis of myocardial cells in rats with acute myocardial infarction. Methods: SD rats were divided into control (Sham group), acute myocardial infarction model rats (AMI group), AMI rats treated by RSV with the dose of 5 mg.kg⁻¹.d⁻¹ (RSV group), AMI rats treated by RSV and AMPK inhibitor Compound C at the same time (RSV+ CC group)(n=8) based on simple random sampling methods. Rat myocardial cell line H9c2 was divided into control group, Hypoxia group, Hypoxia+ RSV group, Hypoxia+ RSV+ Compound C group, Hypoxia+ AICAR (AMPK activator) group. After 6 weeks, the rats were examined by hemodynamics, and pathological observation of myocardial tissue by HE staining was also carried out. RT-PCR/Western blot were used to detect the expression of Beclin1, p62, BAX and Bcl-2 mRNA or protein of different groups in vivo and in vitro. Western blot was used to detect the expression of mTOR and AMPK protein and phosphorylation in cardiac tissue of each group. Results: In this study, the rat model of acute myocardial infarction was successfully prepared. Compared with the AMI group, the myocardium inflammation in the RSV group was alleviated, the LVMI decreased significantly, LVSP increased significantly, LVEDP decreased significantly, HR decreased significantly, the absolute value of dP/dTmax and -dP/dTmax increased significantly. The levels of Beclin1 and Bcl-2 mRNA were significantly up-regulated from 0.43 to 2.01 and 0.30 to 0.72, the expression of p62 and BAX mRNA decreased in half, the phosphorylation level of AMPK was significantly up-regulated, and the level of mTOR phosphorylation significantly reduced (P<0.05). These changes were antagonized by AMPK inhibitors in RSV+ CC group. In vitro experiments showed that, after RSV intervening, the levels of Beclin1 and Bcl-2 mRNA and protein in the myocardial cells of Hypoxia group significantly increased in triple, while the expressions of p62 and BAX mRNA and protein significantly decreased above a half. The above changes were consistent with those of the AMPK activator group and were antagonized by Compound C. Conclusion: RSV can effectively promote autophagy and decrease apoptosis in rat heart after myocardial infarction through AMPK/mTOR pathway.

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