
[2] Brull F, De Smet E, Mensink RP et al. Dietary plant stanol ester consumption improves immune function in asthma patients: results of a randomized, double-blind clinical trial. The American journal of clinical nutrition 2016.BACKGROUND: In vitro and ex vivo studies have suggested that plant sterols and stanols can shift the T helper (Th) 1/Th2 balance toward a Th1-type immune response, which may be beneficial in Th2-dominant conditions such as asthma and allergies. OBJECTIVE: We evaluated in vivo whether plant stanol esters affect the immune response in asthma patients. DESIGN: Fifty-eight asthma patients participated in a randomized, double-blind, placebo-controlled intervention study. All subjects started with a 2-wk run-in period in which they consumed 150 mL control soy-based yogurt without added plant stanol esters/d. Next, an 8-wk experimental period was started in which one-half of the participants received plant stanol enriched soy-based yogurts (4.0 g plant stanols/d), whereas the other one-half of subjects continued the consumption of control yogurts. After 4 wk of daily plant stanol consumption, all participants were vaccinated against hepatitis A virus (HAV), and the increase of antibody titres was monitored weekly until 4 wk after vaccination. RESULTS: Asthma patients in the plant stanol ester group showed higher antibody titres against HAV 3 and 4 wk after vaccination [19% (P = 0.037) and 22% (P = 0.030), respectively]. Also, substantial reductions in plasma total immunoglobulin E, interleukin (IL)-1beta, and tumor necrosis factor-alpha were shown in the plant stanol ester group. The increase in serum plant stanol concentrations was correlated significantly with the decrease in IL-13 concentrations and the Th1 switch in the Th1/Th2 balance. However, no absolute differences in cytokine production between the plant stanol group and the control group were shown. CONCLUSION: To the best of our knowledge, we are among the first authors to show that plant stanol ester consumption improves the immune function in vivo in asthma patients. This trial was registered at clinicaltrials.gov as NCT01715675.Pubmed ID http://www.ncbi.nlm.nih.gov/pubmed/?term=26762374

[3] Reiman A, Pandey S, Lloyd KL et al. ANNALS EXPRESS: Molecular testing for familial hypercholesterolemia-associated mutations in a UK-based cohort: Development of an NGS-based method and comparison with multiplex PCR and oligonucleotide arrays. Annals of clinical biochemistry 2016.BACKGROUND: Detection of disease-associated mutations in patients with familial hypercholesterolemia (FH) is crucial for early interventions to reduce risk of cardiovascular disease. Screening for these mutations represents a methodological challenge since more than 1200 different causal mutations in the LDLR have been identified. A number of methodological approaches have been developed for screening by clinical diagnostic laboratories. METHODS: Using primers targeting the LDLR, APOB and PCSK9, we developed a novel Ion Torrent-based targeted re-sequencing method. We validated this, in a West Midlands-UK small cohort of 58 patients screened in parallel with other mutation-targeting methods, such as multiplex PCR (Elucigene FH20), oligonucleotide arrays (Randox FH array) or the Illumina NGS platform. RESULTS: In this small cohort, the NGS method achieved excellent analytical performance characteristics and showed 100% and 89% concordance with the Randox array and the Elucigene FH20 assay. Investigation of the discrepant results identified 2 cases of mutation misclassification of the Elucigene FH20 multiplex PCR assay. A number of novel mutations not previously reported, were also identified by the NGS method. CONCLUSIONS: Ion Torrent-based NGS can deliver a suitable alternative for the molecular investigation of FH patients, especially when comprehensive mutation screening for rare or unknown mutations is required. KEYWORDS:NGS, FH mutation, molecular screening, LDLR, apoB.Pubmed ID http://www.ncbi.nlm.nih.gov/pubmed/?term=26748104
[4] Schweitzer M, Makhou S, Paliouras M et al. Characterization of the NPC1L1 gene and proteome from an exceptional responder to ezetimibe. *Atherosclerosis* 2015; 246:78-86. BACKGROUND: Strategies to reduce LDL-cholesterol involve reductions in cholesterol synthesis or absorption. We identified a familial hypercholesterolemia patient with an exceptional response to the cholesterol absorption inhibitor, ezetimibe. Niemann-Pick C 1-like 1 (NPC1L1) is the molecular target of ezetimibe. METHODS AND RESULTS: Sequencing identified nucleotide changes predicted to change amino acids 52 (L52P), 300 (I300T) and 489 (S489G) in exceptional NPC1L1. In silico analyses identified increased stability and cholesterol binding affinity in L52P-NPC1L1 versus WT-NPC1L1. HEK293 cells overexpressing WT-NPC1L1 or NPC1L1 harboring amino acid changes singly or in combination (Comb-NPC1L1) had reduced cholesterol uptake in Comb-NPC1L1 when ezetimibe was present. Cholesterol uptake was reduced by ezetimibe in L52P-NPC1L1, I300T-NPC1L1, but increased in S489G-NPC1L1 overexpressing cells. Immunolocalization studies found preferential plasma membrane localization of mutant NPC1L1 independent of ezetimibe. Flotillin 1 and 2 expression was reduced and binding to Comb-NPC1L1 was reduced independent of ezetimibe exposure. Proteomic analyses identified increased association with proteins that modulate intermediate filament proteins in Comb-NPC1L1 versus WT-NPC1L1 treated with ezetimibe. CONCLUSION: This is the first detailed analysis of the role of NPC1L1 mutations in an exceptional responder to ezetimibe. The results point to a complex set of events in which the combined mutations were shown to affect cholesterol uptake in the presence of ezetimibe. Proteomic analysis suggests that the exceptional response may also lie in the nature of interactions with cytosolic proteins. Pubmed ID http://www.ncbi.nlm.nih.gov/pubmed/?term=26761771

[5] Sahebkar A, Rathouska J, Derosa G et al. Statin impact on disease activity and C-reactive protein concentrations in systemic lupus erythematosus patients: A systematic review and meta-analysis of controlled trials. *Autoimmunity reviews* 2015. BACKGROUND AND PURPOSE: Efficacy and safety of statin therapy in patients with systemic lupus erythematosus (SLE) is controversial. The aim of this meta-analysis was to evaluate whether statin therapy affects SLE disease activity and systemic inflammation (C-reactive protein, CRP) according to the evidence from controlled clinical trials. EXPERIMENTAL APPROACH: A systematic review followed by a bibliographic search in Medline and SCOPUS (up to March 2015) was performed. Quantitative data synthesis was performed using a random-effects model and the generic inverse variance weighting method. Effect sizes were expressed as weighted mean difference (WMD) and 95% confidence interval (CI). KEY RESULTS: Meta-analysis of five controlled trials reporting statin impact on SLE disease activity did not suggest any significant effect of statin therapy on SLEDAI. Evaluation of seven controlled trials with reported effects on CRP levels suggested a significant reduction of plasma CRP concentrations in patients with SLE independent of the treatment duration. The effect size on plasma CRP concentrations was significant with lipophilic (atorvastatin) but not hydrophilic (pravastatin and rosuvastatin) statins. CONCLUSION AND IMPLICATIONS: The present results suggest that statin therapy is likely to be safe in patients with SLE. In addition, statin-treated SLE patients may benefit from CRP reduction in terms of managing severe cardiovascular complications associated with the disease. Pubmed ID http://www.ncbi.nlm.nih.gov/pubmed/?term=26747436

[6] Mizoi K, Takahashi M, Haba M, Hosokawa M. Synthesis and evaluation of atorvastatin esters as prodrugs metabolically activated by human carboxylesterases. *Bioorganic & medicinal chemistry letters* 2015. We synthesized 11 kinds of prodrug with an esterified carboxylic acid moiety of atorvastatin in moderate to high yields. We discovered that they underwent metabolic activation specifically by the human carboxylesterase 1 (CES1) isozyme. The results suggested that these ester compounds of
atorvastatin have the potential to act as prodrugs in vivo. PubMed ID

[7] Sayin I, Ayli M, Oguz AK, Cengiz Seval G. Xanthelasma palpebrarum: a new side effect of nilotinib. BMJ case reports 2016; 2016. Chronic myeloid leukaemia (CML) is a chronic myeloproliferative disorder characterised by a reciprocal translocation between the chromosomes 9 and 22 resulting in constitutionally active tyrosine kinase signalling. BCR-ABL tyrosine kinase inhibitors (TKIs) are highly effective molecules in the treatment of CML. Unfortunately, these novel therapeutic agents are accompanied by various side effects, and haematological, cutaneous and metabolic abnormalities are among the most prevalent. Nilotinib, a second-generation TKI, has been shown to cause both-cutaneous lesions and lipid profile abnormalities. We present two CML cases developing xanthelasma palpebrarum while receiving nilotinib. Case 1 also acquired a lipid abnormality following the start of nilotinib therapy, while case 2 meanwhile stayed normolipidemic. In addition to a low cholesterol diet, atorvastatin was prescribed to case 1. Currently, both cases are normolipidemic and continuing their nilotinib therapy. Xanthelasma palpebrarum secondary to nilotinib therapy is new to the literature. PubMed ID

[8] McCully KS. Homocysteine Metabolism, Atherosclerosis, and Diseases of Aging. Comprehensive Physiology 2015; 6:471-505. The importance of homocysteine in vascular function and arteriosclerosis was discovered by demonstration of arteriosclerotic plaques in children with homocystinuria caused by inherited enzymatic deficiencies of cystathionine synthase, methionine synthase, or methylene-tetrahydrofolate reductase. According to the homocysteine theory of arteriosclerosis, an elevated blood homocysteine level is an important risk factor for atherosclerosis in subjects without these rare enzymatic abnormalities. The homocysteine theory is supported by demonstration of arterial plaques in experimental animals with hyperhomocysteinemia, by discovery of a pathway for conversion of homocysteine thiolactone to sulfate in cell cultures from children with homocystinuria, and by demonstration of growth promotion by homocysteic acid in normal and hypophysectomized animals. Studies with cultured malignant cells revealed abnormal homocysteine thiolactone metabolism, resulting in homocysteinylation of proteins, nucleic acids, and glycosaminoglycans, explaining the abnormal oxidative metabolism, abnormalities of cellular membranes, and altered genetic expression observed in malignancy. Abnormal homocysteine metabolism in malignant cells is attributed to deficiency of thioretinamide, the amide synthesized from retinoic acid and homocysteine thiolactone. Two molecules of thioretinamide combine with cobalamin to form thioretinaco. Based on the molecular structure of thioretinaco, a theory of oxidative phosphorylation was proposed, involving oxidation to a disulphonium derivative by ozone, and binding of oxygen, nicotinamide adenine dinucleotide and phosphate as the active site of adenosine triphosphate synthesis in mitochondria. Obstruction of vasa vasorum by aggregates of microorganisms with homocysteinylated low-density lipoproteins is proposed to cause ischemia of arterial wall and a microabscess of the intima, the vulnerable atherosclerotic plaque. (c) 2016 American Physiological Society. Compr Physiol 6:471-505, 2016. PubMed ID

[9] Bassuk SS, Manson JE, Lee IM et al. Baseline characteristics of participants in the VITamin D and Omega-3 Trial (VITAL). Contemporary clinical trials 2016. Evidence for a role of supplemental vitamin D and marine omega-3 fatty acids in preventing cancer and cardiovascular disease (CVD) remains inconclusive and insufficient to inform nutritional recommendations for primary prevention. The VITamin D and Omega-A 3 Trial (VITAL) is an ongoing nationwide, randomized, double-blind, placebo-
controlled clinical trial designed to fill this knowledge gap. The study population consists of 25,874 U.S. adults without cancer or CVD at baseline, who were selected only on age (men aged \geq 50 and women aged \geq 55), with an oversampling of African Americans (n=5107). In a 2x2 factorial design, participants were randomized to one of four supplement groups: [1] active vitamin D3 (cholecalciferol; 2000IU/d) and active marine omega-3 fatty acids (Omacor(R) fish oil, eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA], 1g/d); [2] active vitamin D and omega-3 placebo; [3] vitamin D placebo and active marine omega-3 fatty acids; or [4] vitamin D placebo and omega-3 placebo. The mean length of the randomized treatment period will be 5 years. The randomization was successful, as evidenced by similar distributions of baseline demographic, health, and behavioral characteristics across treatment groups. The similar distribution of known potential confounders across treatment groups strongly suggests that unmeasured or unknown potential confounders are also equally distributed. VITAL is expected to provide important information on the benefit-risk balance of vitamin D and omega-3 fatty acid supplementation when taken for the primary prevention of cancer and CVD. Pubmed ID http://www.ncbi.nlm.nih.gov/pubmed/?term=26767629

[10] Miedema MD, Huguelet J, Virani SS. Aspirin for the Primary Prevention of Cardiovascular Disease: In Need of Clarity. Current atherosclerosis reports 2016; 18:4. Aspirin remains one of the most extensively studied cardiovascular medications in the history of medicine. However, despite multiple, well-designed, large randomized controlled trials evaluating the potential of aspirin to prevent cardiovascular events in individuals without known cardiovascular disease (CVD), the role of aspirin in primary prevention is currently unclear. The initial aspirin trials included largely low-risk individuals with primary outcomes mostly focused on myocardial infarction (MI) and stroke, and showed a significant reduction in these CVD outcomes, especially MI. The more recently conducted trials have focused on older, higher CVD risk populations with high rates of lipid-lowering and antihypertensive medications use. These studies have used broader CVD outcomes as their primary end points and have failed to show a significant benefit of aspirin therapy in primary prevention. The exact reasons for the lack of efficacy in these recent trials are unclear but may be related to low rate of atherothrombotic events relative to other CVD events in the populations studied. Four large randomized controlled trials are currently underway which should provide some clarity in determining the optimal use of aspirin in the primary prevention of CVD. Pubmed ID http://www.ncbi.nlm.nih.gov/pubmed/?term=26753770

[11] Thomson NC. Clinical studies of statins in asthma and COPD. Current molecular pharmacology 2016. Immunomodulatory effects of statins in vitro and in experimental models of asthma and COPD could potentially be relevant to the treatment of chronic airway diseases. This article provides an overview of the evidence from the key clinical studies on the effects of statins on clinical outcomes and inflammatory biomarkers in asthma and COPD. Future directions for clinical studies of statins in asthma and COPD are discussed. A small number of randomized controlled trials (RCTs) in adults with mild to moderate asthma suggest that short-term statin treatment does not improve lung function or symptom control, except for a possible improvement in quality of life and symptoms in smokers with asthma. Several observation studies report that statin use in asthma is associated with a reduced risk of asthma-related emergency department visits, oral corticosteroid dispensing or hospital admissions. Statins treatment in asthma may have modest local anti-inflammatory effects in the airways. There is a need for a large RCTs examining the effects of statins on reducing exacerbations, particularly in severe asthma. In COPD, observational studies suggest that statin use is associated with reduced morbidity and/or mortality, whereas a large RCT concluded that simvastatin did not reduce exacerbations in patients with
COPD that had no cardiovascular indication for statin treatment. It possible that a subgroup of COPD patients with cardiovascular indications for statins and/or systemic inflammation may obtain clinical benefit from statin treatment. Understanding the immunomodulatory effects of statins in asthma and COPD may lead to the development of novel targeted interventions. Pubmed ID http://www.ncbi.nlm.nih.gov/pubmed/?term=26758945

[12] Martin P, Gillen M, Ritter J et al. Effects of Fostamatinib on the Pharmacokinetics of Oral Contraceptive, Warfarin, and the Statins Rosuvastatin and Simvastatin: Results From Phase I Clinical Studies. Drugs in R&D 2016.BACKGROUND AND OBJECTIVES: Fostamatinib is a spleen tyrosine kinase inhibitor that has been investigated as therapy for rheumatoid arthritis and immune thrombocytopenic purpura. The present studies assessed the potential for pharmacokinetic interaction between fostamatinib and the commonly prescribed medications oral contraceptive (OC), warfarin, and statins (rosuvastatin, simvastatin) in healthy subjects. METHODS: The OC study was a crossover study over two 28-day treatment periods (Microgynon(R) 30 plus placebo or fostamatinib). Concentrations of OC constituents (ethinyl estradiol/levonorgestrel) were measured. Effects on warfarin pharmacokinetics and pharmacodynamics were assessed (21-day study). Warfarin was administered on days 1 and 14, fostamatinib on days 8-20. The statin study was a two-period, fixed-sequence study of the effects of fostamatinib on exposure to rosvastatin or simvastatin (single doses). Safety was assessed throughout. RESULTS: Fostamatinib co-administration with OC increased exposure to ethinyl estradiol [area under the plasma concentration-time curve at steady state (AUCss) 28 % [confidence interval (CI) 90 %] 21-36]; maximum plasma concentration (C max) at steady state (C max,ss) 34 % (CI 26-43)], but not levonorgestrel (AUCss 5 %; C max,ss -3 %), while exposure to luteinizing hormone and follicle-stimulating hormone decreased (approximately 20 %). Fostamatinib did not affect the pharmacokinetics/pharmacodynamics of warfarin to a clinically relevant extent, but caused an upward trend in AUC for both R- and S-warfarin [18 % (CI 13-23) and 13 % (CI 7-19)]. Fostamatinib increased rosvastatin AUC by 96 % (CI 78-115) and C max by 88 % (CI 69-110), and increased simvastatin acid AUC by 74 % (CI 50-102) and C max by 83 % (CI 57-113). CONCLUSION: Fostamatinib exhibits drug-drug interactions when co-administered with OC, simvastatin, or rosvastatin, with the AUC of statins almost doubling. Fostamatinib did not exhibit a clinically relevant DDI on warfarin. Pubmed ID http://www.ncbi.nlm.nih.gov/pubmed/?term=26748647

[13] Lee HS, Jung CH, Kim SR et al. Effect of Pitavastatin Treatment on ApoB-48 and Lp-PLA(2) in Patients with Metabolic Syndrome: Sub-study of PROspective Comparative Clinical Study Evaluating the Efficacy and Safety of PITavastatin in Patients with Metabolic Syndrome. Endocrinol Metab (Seoul) 2016.BACKGROUND: Apolipoprotein (Apo) B-48 is an intestinally derived lipoprotein that is expected to be a marker for cardiovascular disease (CVD). Lipoprotein-associated phospholipase A(2) (Lp-PLA(2)) is a vascular-specific inflammatory marker and important risk predictor of CVD. The aim of this study was to explore the effect of pitavastatin treatment and life style modification (LSM) on ApoB-48 and Lp-PLA(2) levels in metabolic syndrome (MS) patients at relatively low risk for cardiovascular disease, as a sub-analysis of a previous multi-center prospective study. METHODS: We enrolled 75 patients with MS from the PROPIT study and randomized them into two treatment groups: 2mg pitavastatin daily + intensive LSM or intensive LSM only. We measured the change of lipid profiles, apolipoproteins and Lp-PLA(2) for 48 weeks. RESULTS: Total cholesterol, LDL cholesterol, Non-HDL cholesterol, and ApoB100/A1 ratio were significantly improved in the pitavastatin + LSM group compared to the LSM only group (P=<0.001). Pitavastatin + LSM did not change the level of ApoB-48 in subjects overall, but the level of ApoB-48 was
significantly lower in the higher mean baseline value group of ApoB-48. The change in Lp-PLA(2) was not significant after intervention in either group after treatment with pitavastatin for 1 year. CONCLUSION: Pitavastatin treatment and LSM significantly improved lipid profiles, ApoB100/A1 ratio, and reduced ApoB-48 levels in the higher mean baseline value group of ApoB-48, but did not significantly alter the Lp-PLA(2) levels. Pubmed ID http://www.ncbi.nlm.nih.gov/pubmed/?term=26754586

[14] Kastelein JJ, Nissen SE, Rader DJ et al. Safety and efficacy of LY3015014, a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 (PCSK9): a randomized, placebo-controlled Phase 2 study. European heart journal 2016. AIMS: The objective of this study was to evaluate the efficacy, safety, and tolerability of LY3015014 (LY), a neutralizing antibody of proprotein convertase subtilisin/kexin type 9 (PCSK9), administered every 4 or 8 weeks in patients with primary hypercholesterolaemia, when added to a background of standard-of-care lipid-lowering therapy, including statins. METHODS AND RESULTS: Double-blind, placebo-controlled trial randomized 527 patients with primary hypercholesterolaemia from June 2013 to January 2014 at 61 community and academic centres in North America, Europe, and Japan. Patients were randomized to subcutaneous injections of LY 20, 120, or 300 mg every 4 weeks (Q4W); 100 or 300 mg every 8 weeks (Q8W) alternating with placebo Q4W; or placebo Q4W. The primary endpoint was percentage change from baseline in low-density lipoprotein cholesterol (LDL-C) by beta quantification at Week 16. The mean baseline LDL-C by beta quantification was 136.3 (SD, 45.0)mg/dL. LY3015014 dose-dependently decreased LDL-C, with a maximal reduction of 50.5% with 300 mg LY Q4W and 37.1% with 300 mg LY Q8W compared with a 7.6% increase with placebo maintained at the end of the dosing interval. There were no treatment-related serious adverse events (AEs). The most common AE terms (>10% of any treatment group) reported more frequently with LY compared with placebo were injection site (IS) pain and IS erythema. No liver or muscle safety issues emerged. CONCLUSIONS: LY3015014 dosed every 4 or 8 weeks, resulted in robust and durable reductions in LDL-C. No clinically relevant safety issues emerged with the administration of LY. The long-term effects on cardiovascular outcomes require further investigation. Pubmed ID http://www.ncbi.nlm.nih.gov/pubmed/?term=26757788


[16] Ellulu MS, Patimah I, Khaza’ai H et al. Atherosclerotic cardiovascular disease: a review of initiators and protective factors. Inflammopharmacology 2016. Atherosclerotic cardiovascular disease (CVD) is a collective term comprising of a group of disorders of the heart and blood vessels. These diseases are the largest cause of morbidity and premature death worldwide. Coronary heart disease and cerebrovascular disease (stroke) are the most frequently occurring diseases. The two major initiators involved in the development of atherosclerotic CVD are vascular production of reactive oxygen species (ROS) and lipid oxidation. In atherosclerosis development, ROS is associated with rapid loss of anti-inflammatory and anti-atherogenic activities of the endothelium-derived nitric oxide (NO) resulting in endothelial dysfunction. In part involving activation of the transcription factor NF-kappaB, ROS have been involved in signaling cascades leading to vascular pro-inflammatory and pro-thrombotic gene expression. ROS is also a potent activator of matrix metalloproteinases (MMPs), which indicate plaque destabilization and rupture. The second initiator involved in atherosclerotic CVD is the oxidation of low-density lipoproteins (LDL). Oxidation of LDL in vessel wall leads to an inflammatory cascade that activates atherogenic pathway leading to foam cell formation. The accumulation of foam cells leads to fatty streak formation, which is the earliest visible atherosclerotic lesion. In contrast, the cardiac sarco/endoplasmic reticulum
Ca\(^{2+}\)-ATPase (SERCA2a) and hepatic apolipoprotein E (apoE) expression can improve cardiovascular function. SERCA2a regulates the cardiac contractile function by lowering cytoplasmic calcium levels during relaxation, and affecting NO. action in vascular cells, while apoE is a critical ligand in the plasma clearance of triglyceride- and cholesterol-rich lipoproteins. 


[17] Castellano JM, Bueno H, Fuster V. The cardiovascular polypill: clinical data and ongoing studies. *International Journal of Cardiology* 2015; 201 Suppl 1:S8-s14. Cardiovascular risk modification in terms of comprehensive medical therapy (antithrombotic therapy, lipid-lowering therapy, antihypertensive medication) and lifestyle modification (healthy diet, regular exercise, weight loss, smoking cessation) is the cornerstone of secondary prevention. It is now clear that even in those undergoing PCI or bypass surgery, appropriate lifestyle modification and aggressive medical therapy are paramount for optimizing long-term outcomes. However, what has emerged from studies that examined the role of medical therapy in the context of coronary heart disease is that only approximately 50% of the patients in these studies are achieving target treatment goals for blood pressure, lipid and glycemic control. Non-adherence is thought to be a very large contributor to this problem; across all health-care categories, non-adherence is estimated to account for $290 billion of annual health-care expenditure in the United States and euro1.25 billion in European Union, with poor adherence to CVD medication accounting for 9% of all European CVD events. Socioeconomic factors may have a role in patients' discontinuing their medications, and a major initiative to combat this problem is the increasing focus on the polypill. The idea of combining numerous medications into a single tablet to reduce CV risk was first proposed more than a decade ago. This combined formulation not only significantly enhances patient convenience and adherence but also drives savings for the healthcare systems. Several randomized clinical trials have consistently demonstrated the effects of polypills on CV risk factors and adherence, and major trials are underway to study the effect on hard clinical outcomes. 


[18] Tamargo J, Castellano JM, Fuster V. The Fuster-CNIC-Ferrer Cardiovascular Polypill: a polypill for secondary cardiovascular prevention. *International Journal of Cardiology* 2015; 201 Suppl 1:S15-22. During the last decade, there has been a tremendous effort to develop different cardiovascular polypills in response to the upsurge in global cardiovascular disease worldwide. The pharmacological development of such a strategy has proven to be extremely complex from a formulation standpoint. Not all drugs are suitable for use in a polypill because of potential drug incompatibilities between them. Candidate agents must be safe, well tolerated, effective, guideline recommended and physiochemically compatible with the other components of the pill. The Fuster-CNIC-Ferrer cardiovascular (CV) polypill has been found to be the first-in-class polypill to be approved and commercialized in Europe and Latinamerican Countries. In this article, we review the pharmacological properties of its three components, including the clinical evidence supporting their use in patients with established cardiovascular disease, their pharmacokinetic properties, adverse effects, drug interactions and contraindications. 


[19] Pourmatroud E, Mohammadjafari R, Roozitalab M. Comparison of Metformin and Simvastatin Administration in Women With Polycystic Ovary Syndrome Before Intra-Cytoplasmic Sperm Injection Cycle: A Prospective, Randomized, Clinical Trial Study. *Iranian Red Crescent Medical Journal* 2015; 17:e20082. BACKGROUND: Drugs administration as a pretreatment regimen before ICSI cycle in PCOs patients could enhance the success rate. OBJECTIVES: The aim of this study was to compare the
effectiveness of metformin with Simvastatin in patients with polycystic ovary syndrome (PCOs) candidates for intra-cytoplasmic sperm injection (ICSI) before starting the cycle. PATIENTS AND METHODS: In this prospective, double blind, randomized clinical trial the efficacy of these drugs was evaluated in 40 women with PCO syndrome (20 patients in each group; A: simvastatin and B: metformin) candidates for ICSI. In the both groups, metformin and simvastatin administrated for eight weeks before starting the ICSI cycle. Endocrine, metabolic and clinical parameters were measured before and after drug therapy; also, the results of ICSI cycle evaluated in the both groups. RESULTS: Both drugs improved hirsutism score significantly, but simvastatin better than metformin (Group A, 24.5 +/- 3.6 P: 0.0001 VS Group B, 22.9 +/- 5.9 P: 0.003). The reduction in body mass index (BMI) was not significant in the groups. Simvastatin reduced some biochemical parameters such as FSH, LH, testosterone, total cholesterol, LDL and increased HDL level significantly, whereas metformin decreased FSH, TG, testosterone and total cholesterol significantly. Overall, respectively 35% and 30% of patients treated with metformin and Simvastatin became pregnant. There was no significant difference between the effects of these two drugs on ICSI cycle results like oocyte in meiosis2 (M2) phase (1.35 +/- 1.6 vs. 2 +/- 3.87, P value: 0.4) and the number of Grade A, embryo (1.2 +/- 1.3 vs. 1.1 +/- 1.4, P value: 0.7). CONCLUSIONS: Simvastatin effectively improved hyperandrogenism signs and symptoms in patients with PCO, but this effect as a pretreatment regimen was not more expressive than metformin in ICSI cycle outcome. Pubmed ID http://www.ncbi.nlm.nih.gov/pubmed/?term=26756007

[20] Jin H, Chen T, Li G et al. Dose-Dependent Neuroprotection and Neurotoxicity of Simvastatin through Reduction of Farnesyl Pyrophosphate in Mice Treated with Intracerebroventricular Injection of Abeta 1 - 42. Journal of Alzheimer's disease : JAD 2016. BACKGROUND: Simvastatin (SV) has been reported to improve dementia and slow progression of Alzheimer's disease (AD), however there are conflicting reports. OBJECTIVE & METHODS: Intracerebroventricular injection of aggregated Abeta 1 - 42 in mice (Abeta 1 - 42-mice) caused spatial cognitive deficits, long-term potentiation (LTP) impairment, and death of hippocampal pyramidal cells. The present study focused on exploring the dose-dependent effects of SV (10-80 mg/kg) on Abeta 1 - 42-impaired spatial memory and the underlying mechanisms. RESULTS: The treatment of Abeta 1 - 42-mice with SV for continuous 15 days could attenuate the spatial cognitive deficits and recover the LTP induction in a "U" type dose-dependent manner. The death of pyramidal cells in Abeta 1 - 42-mice was significantly reduced by the SV-treatment at 20 mg/kg, but not at dose of 10 or 40 mg/kg, even was aggravated at dose of 80 mg/kg. Hippocampal NMDA receptor (NMDAR) NR2B phosphorylation (phospho-NR2B) was elevated in Abeta 1 - 42-mice, which was further dose-dependently increased by SV-treatment. Replenishment of isoprenoid farnesyl pyrophosphate (FPP) by applying farnesol (FOH) could abolish the SV-increased phospho-NR2B in Abeta 1 - 42-mice, but had no effect on the Abeta 1 - 42-enhanced phospho-NR2B. NMDAR antagonist blocked the neurotoxicity of Abeta 1 - 42 and SV (80 mg/kg) in Abeta 1 - 42-mice, whereas FOH only inhibited SV (80 mg/kg)-neurotoxicity. The SV-treatment in Abeta 1 - 42-mice corrected the decrease in hippocampal Akt phosphorylation. The PI3K inhibitor abolished the SV (20 mg/kg)-neuroprotection in Abeta 1 - 42-mice. CONCLUSION: SV-treatment in Abeta 1 - 42-mice exerts dose-dependent neuroprotection and neurotoxicity by reducing FPP to enhance the phosphorylation of NR2B and Akt. Pubmed ID http://www.ncbi.nlm.nih.gov/pubmed/?term=26757191

extent and progression of coronary calcification predict cardiovascular events. Relatively little is known about noncoronary vascular calcification. OBJECTIVES: This study investigated noncoronary vascular calcification and its influence on changes in vascular inflammation. METHODS: A total of 130 participants in the dal-PLAQUE (Safety and efficacy of dalcetrapib on atherosclerotic disease using novel non-invasive multimodality imaging) study underwent fluorodeoxyglucose positron emission tomography/computed tomography at entry and at 6 months. Calcification of the ascending aorta, arch, carotid, and coronary arteries was quantified. Cardiovascular risk factors were related to arterial calcification. The influences of baseline calcification and drug therapy (dalcetrapib vs. placebo) on progression of calcification were determined. Finally, baseline calcification was related to changes in vascular inflammation. RESULTS: Age >65 years old was consistently associated with higher baseline calcium scores. Arch calcification trended to progress more in those with calcification at baseline (p = 0.055). There were no significant differences between progression of vascular calcification with dalcetrapib compared to that with placebo. Average carotid target-to-background ratio indexes declined over 6 months if carotid calcium was absent (single hottest slice [p = 0.037], mean of maximum target-to-background ratio [p = 0.010], and mean most diseased segment [p < 0.001]), but did not significantly change if calcification was present at baseline. CONCLUSIONS: Across multiple arterial regions, higher age is consistently associated with higher calcium scores. The presence of vascular calcification at baseline is associated with progressive calcification; in the carotid arteries, calcification appears to influence vascular inflammation. Dalcetrapib therapy did not affect vascular calcification.


[22] Lee JH, B OH, Han D et al. Reassessing the Usefulness of Coronary Artery Calcium Score among Varying Racial and Ethnic Groups by Geographic Locations: Relevance of the Korea Initiatives on Coronary Artery Calcification Registry. *Journal of cardiovascular ultrasound* 2015; 23:195-203. There is some disparity in the morbidity and mortality rates of cardiovascular disease (CVD) according to race, ethnicity, and geographic regions. Although prediction algorithms that evaluate risk of cardiovascular events have been established using traditional risk factors, they have also demonstrated a number of differences along with race and ethnicity. Of various risk assessment modalities, coronary artery calcium (CAC) score is a sensitive marker of calcific atherosclerosis and correlates well with atherosclerotic plaque burden. Although CAC score is now utilized as a useful tool for early detection of coronary artery disease, prior studies have suggested some variability in the presence and severity of coronary calcification according to race, ethnicity, and/or geographic regions. Among Asian populations, it would appear necessary to reappraise the utility of CAC score and whether it remains superior over and above established clinical risk prediction algorithms. To this end, the Korea initiatives on coronary artery calcification (KOICA) registry has been designed to identify the effectiveness of CAC score for primary prevention of CVD in asymptomatic Korean adults. This review discusses the important role of CAC score for prognostication, while also describing the design and rationale of the KOICA registry.


[23] Kurano M, Tsukamoto K, Kamitsuji S et al. Genome-wide association study of serum lipids confirms previously reported associations as well as new associations of common SNPs within PCSK7 gene with triglyceride. *J Hum Genet* 2016. Previous reports including genome-wide association studies (GWASs) have described associations of serum lipids with genomic variations. In the present study, we examined the association of approximately 2.5 million single-nucleotide polymorphisms (SNPs) from 3041 Japanese healthy volunteers obtained from the Japan Pharmacogenomics Data Science Consortium.
(JPDSC) database with serum lipids. We confirmed the previously reported associations of 14 SNPs in 5 regions for low-density lipoprotein (LDL) cholesterol, 23 SNPs in 12 regions for high-density lipoprotein (HDL) cholesterol, 16 SNPs in 6 regions for triglyceride and 5 SNPs in 1 region for phospholipid. Furthermore, we identified 16 possible novel candidate genes associated with LDL cholesterol, HDL cholesterol or triglycerides, where SNPs had P-values of <1 x 10-5. Further replication analyses of these genes with Korean data revealed significant associations of SNPs located within the PCSK7 gene and triglyceride (Pmeta=7.98 x 10-9 and 1.91 x 10-8 for rs508487 and rs236911, respectively). These associations remained significant even by the conditional analysis adjusting for three neighboring variations associated with triglyceride. Our present data suggest that PCSK7 as well as PCSK9 may be associated with lipids, especially triglyceride, and may serve as a candidate for a new drug target to treat lipid abnormality syndromes. Journal of Human Genetics advance online publication, 14 January 2016; doi:10.1038/jhg.2015.170. Pubmed ID http://www.ncbi.nlm.nih.gov/pubmed/?term=26763881

[24] Boyd JH, Fjell CD, Russell JA et al. Increased Plasma PCSK9 Levels Are Associated with Reduced Endotoxin Clearance and the Development of Acute Organ Failures during Sepsis. *Journal of innate immunity* 2016. PURPOSE: We have recently shown that PCSK9 reduces the clearance of endotoxin and is therefore a critical regulator of the innate immune response during infection. However, plasma PCSK9 levels during human sepsis and their relationship to outcomes are not known. Our objective was to determine the relationship between plasma PCSK9 levels and the rate of endotoxin clearance, and then correlate PCSK9 levels with the development of acute organ failures in a cohort of patients with sepsis. METHODS: Using human hepatocyte cells, we determined the threshold at which PCSK9 is able to reduce Escherichia coli endotoxin uptake by cultured human hepatocytes. In a single-centre observational cohort at St. Paul's Hospital in Vancouver, Canada, we recruited 200 patients who activated our Emergency Department's sepsis protocol and measured plasma PCSK9 and lipid levels at triage and throughout the admission. Outcomes were the development of sepsis-induced cardiovascular or respiratory failure. RESULTS: We reviewed the literature and determined that the normal human range of PCSK9 found in plasma is 170-220 ng/ml, while levels of 250 ng/ml and above reduced E. coli endotoxin clearance in cultured human hepatocytes. In septic patients, the median levels associated with new-onset respiratory and cardiovascular failure were 370 (250-500) and 380 (270-530) ng/ml, respectively, versus 270 (220-380) ng/ml in patients who did not go on to develop any organ failure (p = 0.003 and 0.005, respectively). CONCLUSIONS: Plasma PCSK9 levels are greatly increased in sepsis. At normal levels, PCSK9 has no influence upon hepatocyte bacterial endotoxin clearance, but as levels rise, there is a progressive inhibition of clearance. During sepsis, PCSK9 levels are highly correlated with the development of subsequent multiple organ failure. Inhibition of PCSK9 activity is an attractive target for treating the spectrum of sepsis and septic shock. Pubmed ID http://www.ncbi.nlm.nih.gov/pubmed/?term=26765586

[25] Chretien M, Mbikay M. *60 YEARS OF POMC: From the prohormone theory to proopiomelanocortin and to proprotein convertases (PCSK1 to PCSK9).* *Journal of molecular endocrinology* 2016. POMC, pro-opio-melano-cortin, is a polypeptide expressed in the pituitary and the brain where it is proteolytically processed into peptide hormones and neuropeptides with distinct biological activities. It is the prototype of multipotent prohormones. The prohormone theory was first suggested in 1967 when Chretien and Li discovered -lipotropin (-LPH) and observed that a) it was part of beta-lipotropin (beta-LPH), a larger polypeptide characterized two years earlier and b) its C-terminus was beta-melanocyte-stimulating hormone (beta-MSH). This discovery led them to propose that the lipotropins might be
related biosynthetically to the biologically active beta-MSH in a precursor to end product relationship. The theory was widely confirmed in subsequent years. As we celebrate the fiftieth anniversary of the sequencing of beta-lipotropin, we reflect over the lessons learned from the sequencing of those proteins; we explain their extension to the larger POMC precursor; we examine how the theory of precursor endoproteolysis they inspired became relevant for vast fields in biology; how it led, after a long and arduous search, to the novel proteolytic enzymes called proprotein convertases. This family of nine enzymes plays multifaceted functions in growth, development, metabolism, endocrine and brain functions. Their genetics has provided many insights into health and disease. Their therapeutic targeting is foreseeable in the near future. Thus, what started five decades ago as a theory based on POMC fragments, has opened up novel and productive avenues of biological and medical research, including, for our own current interest, a highly intriguing hypocholesterolemic Gln152His PCSK9 mutation in French Canadian families. Pubmed ID http://www.ncbi.nlm.nih.gov/pubmed/?term=26762158

[26] Li XL, Li H, Zhang M et al. Exosomes derived from atorvastatin-modified bone marrow dendritic cells ameliorate experimental autoimmune myasthenia gravis by up-regulated levels of IDO/Treg and partly dependent on FasL/Fas pathway. Journal of neuroinflammation 2016; 13:8. BACKGROUND: Previously, we have demonstrated that spleen-derived dendritic cells (DCs) modified with atorvastatin suppressed immune responses of experimental autoimmune myasthenia gravis (EAMG). However, the effects of exosomes derived from atorvastatin-modified bone marrow DCs (BMDCs) (statin-Dex) on EAMG are still unknown. METHODS: Immunophenotypical characterization of exosomes from atorvastatin- and dimethylsulfoxide (DMSO)-modified BMDCs was performed by electron microscopy, flow cytometry, and western blotting. In order to investigate whether statin-DCs-derived exosomes (Dex) could induce immune tolerance in EAMG, we administrated statin-Dex, control-Dex, or phosphate-buffered saline (PBS) into EAMG rats via tail vein injection. The tracking of injected Dex and the effect of statin-Dex injection on endogenous DCs were performed by immunofluorescence and flow cytometry, respectively. The number of Foxp3(+) cells in thymuses was examined using immunocytochemistry. Treg cells, cytokine secretion, lymphocyte proliferation, cell viability and apoptosis, and the levels of autoantibody were also carried out to evaluate the effect of statin-Dex on EAMG rats. To further investigate the involvement of FasL/Fas in statin-Dex-induced apoptosis, the underlying mechanisms were studied by FasL neutralization assays. RESULTS: Our data showed that the systemic injection of statin-Dex suppressed the clinical symptoms of EAMG rats. These statin-Dex had immune regulation functions in immune organs, such as the spleen, thymus, and popliteal and inguinal lymph nodes. Furthermore, statin-Dex exerted their immunomodulatory effects in vivo by decreasing the expression of CD80, CD86, and MHC class II on endogenous DCs. Importantly, the therapeutic effects of statin-Dex on EAMG rats were associated with up-regulated levels of indoleamine 2,3-dioxygenase (IDO)/Treg and partly dependent on FasL/Fas pathway, which finally resulted in decreased synthesis of anti-R97-116 IgG, IgG2a, and IgG2b antibodies. CONCLUSIONS: Our data suggest that atorvastatin-induced immature BMDCs are able to secrete tolerogenic Dex, which are involved in the suppression of immune responses in EAMG rats. Importantly, our study provides a novel cell-free approach for the treatment of autoimmune diseases. Pubmed ID http://www.ncbi.nlm.nih.gov/pubmed/?term=26757900

[27] Wang YC, Hsieh TC, Chou CL et al. Risks of Adverse Events Following Coprescription of Statins and Calcium Channel Blockers: A Nationwide Population-Based Study. Medicine (Baltimore) 2016; 95:e2487. Some statins (simvastatin, lovastatin, and atorvastatin) are metabolized by cytochrome P450s 3A4 (CYP3A4). Inhibitors of CYP3A4 including some calcium channel blockers (CCBs) might increase
statin blood concentration, owing to drug-drug interactions. Risk of adverse events such as acute kidney injury might occur following the coprescription of CYP3A4-metabolized statins and CCBs that inhibit CYP3A4. This was a population-based cohort study. The study analyzed data of patients treated between 1997 and 2011, retrieved from Taiwan’s National Health Insurance database. We enrolled 32,801 patients who received coprescription of statins and CCBs that inhibit CYP3A4 (amlodipine, diltiazem, felodipine nicardipine, nifedipine, and verapamil). These patients were divided into 2 groups, according to whether they had received CYP3A4-metabolized statins (lovastatin, simvastatin, and atorvastatin) or non-CYP3A4-metabolized statins (fluvasatin, rosuvastatin, and pitavastatin). These 2 groups were 1:1 matched by age, gender, and Carlson comorbidity index. All outcomes were assessed within 90 days following drug coprescription. In this study, 5857 patients received coprescription of CYP3A4-metabolized statins and CCBs that inhibit CYP3A4. There were no differences in comorbidity or use of antihypertensive drugs between patients who received CYP3A4-metabolized statins and those who received non-CYP3A4-metabolized statins. Patients who received CYP3A4-metabolized statins had significantly higher risk of acute kidney injury (adjusted odds ratio [OR] = 2.12; 95% CI = 1.35-3.35), hyperkalemia (adjusted OR = 2.94; 95% CI = 1.36-6.35), acute myocardial infarction (adjusted OR = 1.55; 95% CI = 1.16-2.07), and acute ischemic stroke (adjusted OR = 1.35; 95% CI = 1.08-1.68) than those who received non-CYP3A4-metabolized statins. This nationwide cohort study demonstrated the increased risk of adverse events following the coprescription of CYP3A4-metabolized statins and CCBs that inhibit CYP3A4. Therefore, it is important to take into account the potential adverse events while coprescribing CYP3A4-metabolized statins and CCBs that inhibit CYP3A4.


[28] Kollerits B, Drechsler C, Krane V et al. Lipoprotein(a) concentrations, apolipoprotein(a) isoforms and clinical endpoints in haemodialysis patients with type 2 diabetes mellitus: results from the 4D Study. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 2016. BACKGROUND: High lipoprotein(a) [Lp(a)] concentrations and low molecular weight (LMW) apolipoprotein(a) [apo(a)] isoforms are associated with cardiovascular disease and mortality in the general population. We examined the association of both with all-cause mortality and cardiovascular endpoints in haemodialysis patients with diabetes mellitus. METHODS: This is a post hoc analysis of the prospective 4D Study (German Diabetes Dialysis Study) that evaluated atorvastatin compared with placebo in 1255 haemodialysis patients with type 2 diabetes mellitus (median follow-up 4 years). The association of natural logarithm-transformed Lp(a) concentrations (increment one unit) and apo(a) isoforms with outcomes was analysed by Cox proportional hazards regression. The influence of age (median 66 years) was evaluated by stratified survival analyses. RESULTS: The median baseline Lp(a) concentration was 11.5 mg/dL (IQR 5.0-41.8). A quarter of patients had at least one LMW apo(a) isoform. Increased Lp(a) concentrations were associated with all-cause mortality in the total group [hazard ratio (HR) 1.09 (95% CI 1.03-1.16), P = 0.004]. LMW apo(a) isoforms were only associated with all-cause mortality in patients <66 years [HR 1.38 (95% CI 1.05-1.80), P = 0.02]. The strongest association for Lp(a) concentrations and LMW apo(a) isoforms was found for death due to infection in patients <66 years [HR 1.39 (95% CI 1.14-1.71), P = 0.001; HR 2.17 (95% CI 1.26-3.75), P = 0.005]. Lp(a) concentrations were also associated with fatal stroke in patients <66 years of age [HR 1.54 (95% CI 1.05-2.24), P = 0.03]. Neither Lp(a) nor LMW apo(a) isoforms were associated with other atherosclerosis-related events. CONCLUSIONS: High Lp(a) concentrations and LMW apo(a) isoforms are risk predictors for all-cause mortality and death due to infection in haemodialysis patients.
with diabetes mellitus. These associations are modified by age. Pubmed ID http://www.ncbi.nlm.nih.gov/pubmed/?term=26754832

[29] Mangge H. Beyond Cholesterol - New Cardiovascular Biomarkers. Nestle Nutrition Institute workshop series 2016; 84:81-88. Atherosclerosis (AS) is the primary pathological result of obesity. Vulnerable AS plaques cause fatal clinical end points such as myocardial infarction and stroke. To prevent this, improvements in early diagnosis and treatment are essential. Because vulnerable AS plaques are frequently nonstenotic, they are preclinically undetectable using conventional imaging. Levels of blood lipids, C-reactive protein, and interleukin-6 are increased, but are insufficient to indicate the process of critical perpetuation before the end points present. More specific biomarkers (e.g. troponin, copeptin, natriuretic peptides, growth differentiation factor-15, or soluble ST2) indicate the acute coronary syndrome or cardiac insufficiency, but not a critical destabilization of AS lesions in coronary or carotid arteries. Thus, valuable time (months to years) that could be used to treat the patient is wasted. An improved management of this dilemma may involve better detection of variations in degrees of immune inflammation in plaques by using new biomarkers in blood and/or within the lesion (molecular imaging). Macrophage and T-cell polarization, and innate and adaptive immune responses (e.g. Toll-like receptors) are involved in this critical process. New biomarkers in these mechanisms include pentraxin 3, calprotectins S100A8/S100A9, myeloperoxidase, adiponectin, interleukins, and chemokines. These proteins may also be candidates for molecular imaging using nuclear (magnetic resonance) imaging tools. Nevertheless, the main challenge remains: which asymptomatic individual should be screened? At which time interval? Intense interdisciplinary research in laboratory medicine (biomarkers), nanomedicine (nanoparticle development), and radiology (molecular imaging) will hopefully address these questions. Pubmed ID http://www.ncbi.nlm.nih.gov/pubmed/?term=26764476


[31] Lampi MC, Faber CJ, Huynh J et al. Simvastatin Ameliorates Matrix Stiffness-Mediated Endothelial Monolayer Disruption. PloS one 2016; 11:e0147033. Arterial stiffening accompanies both aging and atherosclerosis, and age-related stiffening of the arterial intima increases RhoA activity and cell contractility contributing to increased endothelium permeability. Notably, statins are 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors whose pleiotropic effects include disrupting small GTPase activity; therefore, we hypothesized the statin simvastatin could be used to attenuate RhoA activity and inhibit the deleterious effects of increased age-related matrix stiffness on endothelial barrier function. Using polyacrylamide gels with stiffnesses of 2.5, 5, and 10 kPa to mimic the physiological stiffness of young and aged arteries, endothelial cells were grown to confluence and treated with simvastatin. Our data indicate that RhoA and phosphorylated myosin light chain activity increase with matrix stiffness but are attenuated when treated with the statin. Increases in cell contractility, cell-cell junction size, and indirect measurements of intercellular tension that increase with matrix stiffness, and are correlated with matrix stiffness-dependent increases in monolayer permeability, also decrease with statin treatment. Furthermore, we report that simvastatin increases activated Rac1 levels that contribute to endothelial barrier enhancing cytoskeletal reorganization. Simvastatin, which is prescribed clinically due to its ability to lower cholesterol, alters the endothelial cell response to increased matrix stiffness to restore endothelial monolayer barrier function, and
therefore, presents a possible therapeutic intervention to prevent atherogenesis initiated by age-related arterial stiffening. Pubmed ID http://www.ncbi.nlm.nih.gov/pubmed/?term=26761203

[32] Cariou B. [A YOUNG MAN WHOSE LDL-CHOLESTEROL IS GREATER THAN 1.9 G/L]. Rev Prat 2015; 65:1062-1066. Familial hypercholesterolemia (FH) is both a frequent (estimated prevalence of heterozygous FH: 1/200 to 1/500) and underdiagnosed (< 5 V of diagnosed FH in most countries) genetic disease. Non-treated FH is associated with an increased risk of coronary heart disease (CHD) linked to premature atherosclerosis. The diagnosis of FH should be considered when a subject presents with plasma LDL-cholesterol (LDL-C) level > 190 mg/dl (4.9 mmol/l), premature CHO, tendon xanthomas, familial history of hyperGholerolemia, premature CHD or cardiac death. Cascade screening and genetic analysis help to identify affected relatives. The therapeutic objective is to obtain LDL-C target < 130 mg/dl in young adults without additional cardiovascular risk factors, < 100 mg/dL in the majority of FH patients and < 70 mg/dL in adults with known CHD. Therapeutic management is based on the combination on lifestyle and dietary counselling and pharmacological approaches with maximal potent statin dose, ezetimibe and bile acid sequestrants. In a near future, PCSK9 inhibitors should be a valuable option in FH patients not at LDL-C goal. Pubmed ID http://www.ncbi.nlm.nih.gov/pubmed/?term=26749708

[33] Palmer SC, Navaneethan SD, Craig JC et al. HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis. Sao Paulo medical journal = Revista paulista de medicina 2015; 133:541-542. BACKGROUND: Cardiovascular disease (CVD) is the most frequent cause of death in people with early stages of chronic kidney disease (CKD), for whom the absolute risk of cardiovascular events is similar to people who have existing coronary artery disease. This is an update of a review published in 2009, and includes evidence from 27 new studies (25,068 participants) in addition to the 26 studies (20,324 participants) assessed previously; and excludes three previously included studies (107 participants). This updated review includes 50 studies (45,285 participants); of these 38 (37,274 participants) were meta-analysed. OBJECTIVES: To evaluate the benefits (such as reductions in all-cause and cardiovascular mortality, major cardiovascular events, MI and stroke; and slow progression of CKD to end-stage kidney disease (ESKD)) and harms (muscle and liver dysfunction, withdrawal, and cancer) of statins compared with placebo, no treatment, standard care or another statin in adults with CKD who were not on dialysis. METHODS: SEARCH METHODS: We searched the Cochrane Renal Group’s Specialised Register to 5 June 2012 through contact with the Trials' Search Co-ordinator using search terms relevant to this review. SELECTION CRITERIA: Randomised controlled trials (RCTs) and quasi-RCTs that compared the effects of statins with placebo, no treatment, standard care, or other statins, on mortality, cardiovascular events, kidney function, toxicity, and lipid levels in adults with CKD not on dialysis were the focus of our literature searches. DATA COLLECTION AND ANALYSIS: Two or more authors independently extracted data and assessed study risk of bias. Treatment effects were expressed as mean difference (MD) for continuous outcomes (lipids, creatinine clearance and proteinuria) and risk ratio (RR) for dichotomous outcomes (major cardiovascular events, all-cause mortality, cardiovascular mortality, fatal or non-fatal myocardial infarction (MI), fatal or non-fatal stroke, ESKD, elevated liver enzymes, rhabdomyolysis, cancer and withdrawal rates) with 95% confidence intervals (CI). MAIN RESULTS: We included 50 studies (45,285 participants): 47 studies (39,820 participants) compared statins with placebo or no treatment and three studies (5547 participants) compared two different statin regimens in adults with CKD who were not yet on dialysis. We were able to meta-analyse 38 studies (37,274 participants). The risk of bias in the included studies was high. Seven studies comparing
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Statins with placebo or no treatment had lower risk of bias overall; and were conducted according to published protocols, outcomes were adjudicated by a committee, specified outcomes were reported, and analyses were conducted using intention-to-treat methods. In placebo or no treatment controlled studies, adverse events were reported in 32 studies (68%) and systematically evaluated in 16 studies (34%). Compared with placebo, statin therapy consistently prevented major cardiovascular events (13 studies, 36,033 participants; RR 0.72, 95% CI 0.66 to 0.79), all-cause mortality (10 studies, 28,276 participants; RR 0.79, 95% CI 0.69 to 0.91), cardiovascular death (7 studies, 19,059 participants; RR 0.77, 95% CI 0.69 to 0.87) and MI (8 studies, 9018 participants; RR 0.55, 95% CI 0.42 to 0.72). Statins had uncertain effects on stroke (5 studies, 8658 participants; RR 0.62, 95% CI 0.35 to 1.12). Potential harms from statin therapy were limited by lack of systematic reporting and were uncertain in analyses that had few events: elevated creatine kinase (7 studies, 4514 participants; RR 0.84, 95% CI 0.20 to 3.48), liver function abnormalities (7 studies, RR 0.76, 95% CI 0.39 to 1.50), withdrawal due to adverse events (13 studies, 4219 participants; RR 1.16, 95% CI 0.84 to 1.60), and cancer (2 studies, 5581 participants; RR 1.03, 95% CI 0.82 to 1.30). Statins had uncertain effects on progression of CKD. Data for relative effects of intensive cholesterol lowering in people with early stages of kidney disease were sparse. Statins clearly reduced risks of death, major cardiovascular events, and MI in people with CKD who did not have CVD at baseline (primary prevention). AUTHORS' CONCLUSIONS: Statins consistently lower death and major cardiovascular events by 20% in people with CKD not requiring dialysis. Statin-related effects on stroke and kidney function were found to be uncertain and adverse effects of treatment are incompletely understood. Statins have an important role in primary prevention of cardiovascular events and mortality in people who have CKD. Pubmed ID http://www.ncbi.nlm.nih.gov/pubmed/?term=26760127