HMG-CoA Reductase Inhibitors (Statins) and Fixed-Dose Combination Products Containing a Statin

Preliminary Scan Report #6

March 2018

This report is intended only for state employees in states participating in the Drug Effectiveness Review Project (DERP). Do not distribute outside your state Medicaid agency and public agency partners.

Authors:
Ian Blazina, MPH
Chandler Weeks, BS
Frances Hsu, MPH
Marian McDonagh, PharmD

Conflict of Interest Disclosures:
No authors have conflicts of interest to disclose. All authors have completed and submitted the Oregon Health & Science University form for Disclosure of Potential Conflicts of Interest, and none were reported.

Objective

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant to assist with Participating Organizations' consideration of allocating resources toward a full report update, a single drug addendum, or a summary review. Comprehensive review, quality assessment, and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses on new randomized controlled trials and comparative effectiveness reviews as well as actions taken by the U.S. Food and Drug Administration (FDA) since the last report. Other important studies could exist.

Dates of Previous Original and Update Reports

Update #5: November 2009 (searches through June 2009)
Update #4: August 2006
Update #3: September 2005
Update #2: March 2004
Update #1: July 2003
Original Report: April 2002

Dates of Previous Scan Reports

Scan #6: March 2017
Expanded Scan (Scan #5): January 2016
Scan #4: April 2015
Scan #3: August 2014
Scan #2: August 2013
Scan #1: March 2011

Scope and Key Questions

The scope of the review and key questions were originally developed and refined by the Pacific Northwest Evidence-based Practice Center with input from a statewide panel of experts (pharmacists, primary care clinicians, and representatives of the public). Subsequently, the key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The Participating Organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The Participating Organizations approved the following key questions to guide this review:

1. How do statins and fixed-dose combination products containing a statin and another lipid lowering drug compare in their ability to reduce LDL-C?

   a. Are there doses for each statin or fixed-dose combination product containing a statin and another lipid lowering drug that produce similar percent reduction in LDL-C between statins?
   b. Is there a difference in the ability of a statin or fixed-dose combination product containing a statin and another lipid lowering drug to achieve National Cholesterol Education Panel goals?

2. How do statins and fixed-dose combination products containing a statin and another lipid lowering drug compare in their ability to raise HDL-C?
   a. Are there doses for each statin or fixed-dose combination product containing a statin and another lipid lowering drug that produce similar percent increase in HDL-C between statins?
   b. Is there a difference in the ability of a statin or fixed-dose combination product containing a statin and another lipid lowering drug to achieve National Cholesterol Education Panel goals?

3. How do statins and fixed-dose combination products containing a statin and another lipid lowering drug compare in their ability to reduce the risk of nonfatal myocardial infarction, coronary heart disease (angina), coronary heart disease mortality, all-cause mortality, stroke, hospitalization for unstable angina, or need for revascularization (coronary artery bypass graft, angioplasty, or stenting)?
4. Are there differences in effectiveness of statins and fixed-dose combination products containing a statin and another lipid lowering drug in different demographic groups or in patients with comorbid conditions (e.g., diabetes, obesity)?

5. Are there differences in the harms of statins or fixed-dose combination products containing a statin and another lipid lowering drug when used in the general population of children or adults?

6. Are there differences in the harms of statins or fixed-dose combination products containing a statin and another lipid lowering drug when used in special populations or with other medications (drug-drug interactions)? In addressing this question, we will focus on the following populations:
   a. Patients with HIV
   b. Organ transplant recipients
   c. Patients at high risk for myotoxicity (e.g., patients with a history of statin-associated muscle-related harms due to drug-drug/drug-food interactions, patients co-administered fibrates, patients taking potent 3A4 inhibitors, elderly patients, especially elderly females)
   d. Patients at high risk for hepatotoxicity
   e. Patients using fibrates (gemfibrozil, fenofibrate, fenofibric acid) or niacin
   f. Children with nephrotic syndrome

Methods Summary

We followed standard methodology developed for Drug Effectiveness Review Project (DERP).[13] Detailed methods are available upon request.

Inclusion Criteria

Populations

- Outpatients targeted for primary or secondary prevention of coronary heart disease or non-coronary forms of atherosclerotic disease with or without hypercholesterolemia.
- Inpatients with acute coronary syndrome or undergoing revascularization (if the statin was continued after hospital discharge and if health outcomes were reported).
- Familial hypercholesterolemia (homozygous or heterozygous)
- Both children and adults will be included.
- *Exclusions:* adults with rare, severe forms of hypercholesterolemia (LDL-C ≥ 250mg/dL).

Comparators: Effectiveness and harms of individual statins

- Head-to-head trials comparing one statin to another.

Comparators: Effectiveness and harms of fixed-dose combination products containing a statin

- Head-to-head trials comparing one fixed-dose combination product to another.
- Trials comparing a fixed-dose combination product to an individual statin.
- *Exclusions:* Trials comparing a fixed-dose combination product to the product's individual components given separately (co-administration).

Table 1. Individual statins

Active ingredient	Brand name
Atorvastatin	Lipitor
Fluvastatin	Lescol
Fluvastatin extended release	Lescol XL
Lovastatin	Generic

Table 2. Fixed-dose combination products containing a statin

Active ingredient	Brand name
Atorvastatin; ezetimibe	Liptruzet
Lovastatin; niacin extended release	Advicor
Simvastatin; ezetimibe	Vytorin
Simvastatin; niacin extended release	Simcor

Literature Search

To identify relevant citations, we searched Ovid MEDLINE® ,Ovid MEDLINE® In-Process & Other Non-Indexed Citations, and Cochrane Central Registry of Controlled Trials from January 2016 through February 2018 using terms for specific included drugs and limits for English language and humans. We also searched the FDA website (http://www.fda.gov/medwatch/safety.htm) for identification of new drugs, new populations, and new serious harms (e.g., boxed warnings). To identify new drugs, we conducted an Internet search. To identify comparative effectiveness reviews, we searched the websites of the Agency for Healthcare Research and Quality (http://www.ahrq.gov/) (http://www.effectivehealthcare.ahrq.gov/), the Canadian Agency for Drugs and Technology in Health (http://www.cadth.ca/), the VA Evidence-based Synthesis Program (http://www.hsrd.research.va.gov/publications/esp/reports.cfm), and University of York Centre for Reviews and Dissemination (http://www.york.ac.uk/inst/crd/crdreports.htm - "Our Publications" and "Our Databases"). All citations were imported into an electronic database (EndNote X7) and duplicate citations were removed.

Study Selection

We included only potentially relevant randomized controlled trials and comparative effectiveness reviews. One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

New Drugs

Identified in this Preliminary Update Scan

New Formulations

None

Identified in previous Preliminary Update Scans

Simvastatin oral suspension: approved on 4/21/2016 in 20 mg/5mL and 40 mg/5mL doses.

Atorvastatin/ezetimibe (Liptruzet®): FDA approved a new fixed dose combination product comprised of atorvastatin and ezetimibe on 5/3/2013 for the treatment of hyperlipidemia.

Pitavastatin (Livalo®) was FDA approved in August 2009 as an adjunctive therapy to diet to reduce elevated total cholesterol, low-density lipoprotein cholesterol, apolipoprotein B, and triglycerides, and to increase high-density lipoprotein cholesterol.

New Serious Harms (e.g., Boxed Warnings)

Identified in this Preliminary Update Scan

None

Identified in previous Preliminary Update Scans

None

Comparative Effectiveness Reviews

Identified in this Preliminary Update Scan

None

Identified in previous Preliminary Update Scan(s)

Since the last full update report, we identified 1 comparative effectiveness review published within the last 3 years. This was a 2016 AHRQ Evidence-based Practice Center report on statin use for the prevention of cardiovascular disease in adults. It covers only part of the scope of the DERP report. The citation is listed below and the abstract is available upon request.

> Chou R, Dana T, Blazina I, et al. Statin Use for the Prevention of Cardiovascular Disease in Adults: A Systematic Review for the U.S. Preventive Services Task Force [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2016 Nov. (Evidence Syntheses, No. 139.) 1, Introduction. Available from: https://www.ncbi.nlm.nih.gov/books/NBK396417/

Randomized Controlled Trials

Trials identified since the most recent Full Report

Medline searches resulted in 849 citations. Of those, there were 11 new potentially relevant head-to-head trials and 1 secondary analysis of a head-to-head trial. Three of the new primary head-to-head trials evaluated pitavastatin (seven cumulatively), a new drug approved since the last report. Five new primary head-to-head trials evaluated the newly approved atorvastatin/ezetimibe combination drug. Three of the new primary head-to-head trials report long-term cardiovascular outcomes, with the rest reporting intermediate lipid outcomes. The new secondary analysis compares pitavastatin with pravastatin in subjects with HIV.

Cumulatively, we have identified 55 primary head-to-head trials and 17 secondary analyses of head-to-head trials. Six of the primary head-to-head trials and 8 of the secondary analyses of head-to-head trials report long-term cardiovascular outcomes, with the remainder of the studies reporting intermediate lipid outcomes. Seventeen trials evaluated the new drug pitavastatin and 8 trials evaluated the new atorvastatin/ezetimibe fixed-dose combination product, with the rest of the studies evaluating older statins. Characteristics of these trials are shown in Tables 3 and 4, below. Abstracts for these trials are available in Appendix B.

Table 3. Head-to-head trials (N=55)

Author Year	Comparison	Population	Outcome
Long-term outcomes			
de Zeeuw 2015	Atorvastatin vs rosuvastatin	Patients with progressive renal disease	Harms only (renal effects)
Im, 2017	Pravastatin vs. atorvastatin	Patients undergoing drug-eluting stent implantation	Composite of death, MI, revascularization, stent

			thrombosis, stroke, renal deterioration, intervention for PAD, or admission for cardiac event
Izawa, 2015	Pravastatin vs atorvastatin	Acute myocardial infarction	Composite of all-cause death, non-fatal MI, non-fatal stroke, unstable angina or CHF requiring hospital admission, or any type of coronary revascularization
Japaridze, 2016; Japaridze, 2017	Atorvastatin/ezetimibe vs. atorvastatin	Acute coronary syndrome	Composite of cardiovascular death, nonfatal MI, unstable angina, revascularization, and nonfatal stroke
Liu, 2017	Atorvastatin/ezetimibe vs. atorvastatin	Elderly patients with ACS	Composite of cardiac death, MI, and unplanned revascularization
Sardella 2013	Atorvastatin vs rosuvastatin	Patients with stable angina undergoing elective PCI	Occurrence of major cardiac and cerebrovascular events
Intermediate outcomes (lipids)			
Abe 2015	Pitavastatin vs rosuvastatin	Dyslipidemic patients with chronic kidney disease	LDL-C
Araujo 2010	Simvastatin vs simvastatin + ezetimibe	Hypercholesterolemia	LDL-C
Arimura 2012	Atorvastatin vs atorvastatin/ezetimibe	Patients with stable angina undergoing coronary stent implantation	LDL-C
Bando, 2016	Atorvastatin vs. rosuvastatin	Japanese patients with hypercholesterolemia	LDL-C
Constance 2014	Atorvastatin/ezetimibe vs atorvastatin	Subjects >65 years with high cholesterol and high CHD risk	LDL-C
Eriksson 2011	Pitavastatin vs simvastatin	Primary hypercholesterolemia or combined dyslipidemia and at least two CHD risk factors	LDL-C
Florentin	Simvastatin vs	Primary hypercholesterolemia	LDL-C

2011	simvastatin/ezetimibe		
Foody 2010	Ezetimibe/simvastatin vs atorvastatin	Hypercholesterolemic patients ≥ 65 years ± cardiovascular disease	LDL-C
Gumprecht 2011	Pitavastatin vs atorvastatin	Type 2 diabetes and dyslipidemia	LDL-C
Hall 2009	Rosuvastatin vs simvastatin 40 mg	Hyperlipidemia	LDL-C
Han 2012	Pitavastatin vs atorvastatin	Hypercholesterolemic patients with elevated serum alanine transaminase	LDL-C
Hongo 2011	Rosuvastatin vs fluvastatin	Japanese patients with dyslipidemia	LDL/HDL ratio
Kakuda, 2014	Atorvastatin vs pitavastatin vs rosuvastatin	Dyslipidemia	LDL-C, HDL-C
Kasmas 2012	Rosuvastatin vs simvastatin/ezetimibe	NR	LDL-C
Koksal 2011	Atorvastatin vs rosuvastatin	Type 2 diabetes with LDL-C > 100 mg/dl	LDL-C
Kurogi 2013	Pitavastatin vs atorvastatin	Stable CAD, hypercholesterolemia, and low HDL	HDL-C
Lablanche 2010	Rosuvastatin vs atorvastatin	Acute coronary syndrome	LDL-C
Lee 2013	Ezetimibe/simvastatin vs atorvastatin	Korean patients with type 2 diabetes and LDL-C > 100 mg/dl	LDL-C, HDL-C
Masuda 2015	Rosuvastatin/ezetimibe vs rosuvastatin	Stable coronary artery disease requiring PCI	LDL-C
Matsushita, 2016	Pitavastatin vs. atorvastatin	Patients with ACS	LDL-C
Moreira 2014	Rosuvastatin vs ezetimibe/simvastatin	Hyperlipidemic subjects	Electronegative LDL
Moutzouri 2013	Simvastatin/ezetimibe vs simvastatin vs rosuvastatin	Dyslipidemia	Lipid levels
Murrow 2012	Pravastatin vs atorvastatin	Hyperlipidemia and metabolic syndrome and/or diabetes	LDL-C

Nicholls 2011	Atorvastatin vs rosuvastatin 40 mg	CHD	LDL-C
Nicholls, 2017	Atorvastatin/ezetimibe vs. atorvastatin	Patients with CAD and/or diabetes	LDL-C
Nohara 2012	Rosuvastatin vs pravastatin	Adults with hypercholesterolemia and thickened carotid intima-media	LDL-C/HDL-C ratio
Nozue, 2016	Pitavastatin vs. pravastatin	Statin-naïve patients with CAD	LDL-C
Ogawa 2014	Rosuvastatin vs atorvastatin	Hyperlipidemia and type 2 diabetes	Non-HDL-C
Ose 2009	Pitavastatin vs simvastatin	Primary hypercholesteremia or combined dyslipidemia	LDL-C
Pytel, 2017	Rosuvastatin vs. atorvastatin vs. atorvastatin/ezetimibe	Patients with CAD and healthy patients	LDL-C, HDL-C
Ramos 2011	Rosuvastatin vs simvastatin/ezetimibe vs	Primary hypercholesterolemia	LDL-C, HDL-C
Rosen 2013	Ezetimibe/simvastatin vs simvastatin or atorvastatin vs rosuvastatin	Subjects with cardiovascular disease and diabetes	LDL-C
Saku 2011	Atorvastatin vs rosuvastatin vs pitavastatin	Patients with risk factors for CAD and elevated LDL-C	LDL-C
Sasaki 2013	Pravastatin vs atorvastatin	Men aged > 20 years; postmenopausal women with glucose intolerance	LDL-C, HDL-C
Scheffer 2013	Atorvastatin vs simvastatin	Statin-naïve patients with diabetes and/or obesity and/or hypertension	LDL-C
Shimabukuro 2011	Pitavastatin vs atorvastatin	Type 2 diabetes with hypercholesterolemia and/or triglyceridemia	LDL-C, HDL-C
Shioji 2014	Atorvastatin vs rosuvastatin	Japanese patients with or at risk of CAD	LDL-C
Sponseller 2014	Pitavastatin vs pravastatin	Primary hyperlipidemia or mixed dyslipidemia	LDL-C
Stender 2013	Pitavastatin vs pravastatin	Elderly patients with hypercholesterolemia or dyslipidemia	LDL-C

Tani 2015	Pitavastatin vs atorvastatin	Hypercholesterolemia	LDL-C, HDL-C
Thongtang, 2017	Atorvastatin vs. simvastatin	T2DM patients without CAD	LDL-C
Toribio, 2017	Pitavastatin vs. pravastatin	HIV patients with dyslipidemia	LDL-C
Toyama 2011	Rosuvastatin vs atorvastatin	CAD	HDL-C
Uemura 2012	Atorvastatin/ezetimibe vs atorvastatin	Japanese patients with abnormal glucose tolerance and CAD	LDL-C
Wang, 2017	Atorvastatin/ezetimibe vs atorvastatin	Carotid atherosclerosis, T2DM, and CAD	LDL-C
Watanabe 2015	Pitavastatin vs pravastatin	Patients with atherosclerotic plaque	LDL-C
West 2011	Simvastatin vs simvastatin/ezetimibe	Peripheral arterial disease	LDL-C
Yamamoto 2014	Pravastatin vs rosuvastatin	Patients undergoing placement of drug-eluting stent	LDL-C
Yanagi 2011	Rosuvastatin vs pitavastatin	Japanese type 2 diabetes patients with hyperlipidemia	LDL-C, HDL-C

Table 4. Secondary analyses of head-to-head trials (N=17)

Author Year	Comparison	Population	Outcome	Previously included trial
Long-term outcomes				
Gibson 2009	Atorvastatin vs pravastatin	Acute coronary syndrome, undergoing PCI	Major adverse cardiovascular events	PROVE-IT
Murphy 2009	Atorvastatin vs pravastatin	Acute coronary syndrome	Recurrent cardiovascular events	PROVE-IT
Murphy 2016	Ezetimibe/simvastatin vs simvastatin	Acute coronary syndrome	CV death, MI, stroke, unstable angina leading to hospitalization, coronary	IMPROVE-IT

			revascularization	
Pedersen 2010	Atorvastatin vs simvastatin	Post-MI	Cardiovascular events after 5 years	IDEAL
Sarma 2014	Atorvastatin vs pravastatin	After acute coronary syndrome	Kidney injury (adverse event)	PROVE IT-TIMI 22
Stoekenbroek 2014	Atorvastatin vs simvastatin	Patients with prior MI	Peripheral artery disease, major coronary events, coronary revascularization	IDEAL
Tikkanen 2013	Atorvastatin vs simvastatin	CHD patients ± elevated ALT	Cardiovascular, cerebrovascular events	IDEAL
Truong 2011	Atorvastatin vs pravastatin	Women	Death, MI, unstable angina, revascularization, or stroke	PROVE IT-TIMI 22
Intermediate outcomes (lipids)				
Bohula, 2015	Ezetimibe/simvastatin vs simvastatin	Patients stabilized after acute coronary syndrome	LDL-C	IMPROVE-IT
Joshi, 2017	Pitavastatin vs. pravastatin	Subjects with HIV	LDL-C, HDL-C	INTREPID
Lee 2012a	Atorvastatin vs rosuvastatin	Statin naïve patients with mild coronary atherosclerosis	Lipid levels	ARTMAP
Olsson 2011	Simvastatin vs atorvastatin	CVD	LDL-C	IDEAL
Pitt 2012	Rosuvastatin vs atorvastatin	Adults with CAD	LDL-C	LUNAR
Puri 2013	Rosuvastatin vs atorvastatin	Patients with coronary atherosclerosis ± diabetes	LDL-C, HDL-C	SATURN
Rosen 2013	Ezetimibe/simvastatin vs simvastatin or atorvastatin vs	Diabetic subjects with or without	LDL-C	Trial not specified

	rosuvastatin	obesity		
Stegman 2014	Rosuvastatin vs atorvastatin	Patients with coronary atherosclerosis ± diabetes	LDL-C, HDL-C	SATURN
Yokoi 2014	Rosuvastatin vs pravastatin	Patients with elevated LDL-C and thickened carotid intima-media	LDL-C	JART

Summary

Since the last update report, we have identified 1 newly approved drug (pitavastatin), 1 newly approved drug combination (atorvastatin/ezetimibe), and 1 new formulation for an existing drug (simvastatin oral suspension). Pitavastatin and the combination drug of atorvastatin/ezetimibe were included in the Expanded Scan conducted in January 2016. We have identified 1 new comparative effectiveness review that is current and related to this topic. In terms of new trial evidence, we have identified 55 new primary head-to-head trials (11 new this scan) and 17 secondary analyses of head-to-head trials (1 new this scan) since the last update report on this topic.

APPENDIX A. NEW COMPARATIVE EFFECTIVENESS REVIEWS

Chou R, Dana T, Blazina I, et al. **Statin Use for the Prevention of Cardiovascular Disease in Adults: A Systematic Review for the U.S. Preventive Services Task Forc**e [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2016 Nov. (Evidence Syntheses, No. 139.) 1, Introduction. Available from: https://www.ncbi.nlm.nih.gov/books/NBK396417/

Structured Abstract
Background: Cardiovascular disease (CVD) is the leading cause of mortality and morbidity in the United States but is potentially preventable with statin therapy. The U.S. Preventive Services (USPSTF) commissioned this review to inform the development of new recommendations on use of statin therapy for prevention of CVD in adults.

Purpose: To evaluate benefits and harms of statin therapy for prevention of CVD in adults without prior cardiovascular events.

Data Sources: We searched the Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and MEDLINE to June 2016 and manually reviewed reference lists.

Study Selection: Randomized, controlled trials on the benefits and harms of statin therapy versus placebo or no statin in adults without prior cardiovascular events.

Data Extraction: One investigator abstracted data and a second investigator checked data abstraction for accuracy. Two investigators independently assessed study quality using methods developed by the USPSTF.

Data Synthesis (Results): Nineteen trials with followup from 6 months to 6 years compared statin therapy versus placebo or no statin. Statin therapy was associated with decreased risk of all-cause mortality (risk ratio [RR], 0.86 [95% CI, 0.80 to 0.93]; absolute risk difference [ARD], -0.40%; number needed to treat [NNT], 250), cardiovascular mortality (RR, 0.69 [95% CI, 0.54 to 0.88]; ARD, -0.43%; NNT, 233), stroke (RR, 0.71 [95% CI, 0.62 to 0.82]; ARD, -0.38%; NNT, 263), myocardial infarction (RR, 0.64 [95% CI, 0.57 to 0.71]; ARD, -0.81%; NNT, 123), and composite cardiovascular outcomes (RR, 0.70 [95% CI, 0.63 to 0.78]; ARD, -1.39%; NNT, 72). Relative benefits appeared to be consistent in subgroups defined by demographic and clinical characteristics, including populations with cardiovascular risk factors without marked hyperlipidemia. Statin therapy was not associated with significantly increased risk of serious adverse events (RR, 0.99 [95% CI, 0.94 to 1.04]), myalgia (RR, 0.96 [95% CI, 0.79 to 1.16]), or liver-related harms (RR, 1.10 [95% CI, 0.90 to 1.35]). Statins were not associated with increased risk of diabetes (RR, 1.05 [95% CI, 0.91 to 1.20]), though statistical heterogeneity was present (I^2 =52%), and one trial found that high-intensity statins were associated with increased risk (RR, 1.25 [95% CI, 1.05 to 1.49]). No trial directly compared titrated versus fixed-dose statin therapy. Based on an analysis of individual patient data from randomized trials, greater reductions in lowdensity lipoprotein cholesterol levels with statin therapy are associated with reduced risk of

CVD events, which may provide some indirect evidence that higher-intensity therapy may be associated with better clinical outcomes than lower-intensity therapy.

Limitations: Restricted to English language, statistical heterogeneity in some pooled analyses, and limited formal assessment for publication bias.

Conclusions: In adults at increased CVD risk but without prior CVD events, statin therapy is associated with reduced risk of all-cause and cardiovascular mortality and CVD events. Benefits appear to be present across diverse demographic and clinical subgroups, with greater absolute benefits in patients at higher baseline risk, and do not appear to be restricted to patients with marked hyperlipidemia.

APPENDIX B. NEW HEAD-TO-HEAD TRIALS OF STATINS (HEALTH AND LIPID OUTCOMES)

Abe, M., et al. (2015). A Trial of Pitavastatin Versus Rosuvastatin for Dyslipidemia in Chronic Kidney Disease. Journal of Atherosclerosis & Thrombosis. **22:** 1235-1247.

AIM: To determine the lipid lowering effectiveness, cost effectiveness, and safety of rosuvastatin compared with pitavastatin in dyslipidemic patients with concurrent renal disorders.

METHODS: This single-center, prospective, open-label, randomized, 12-month study evaluated rosuvastatin (2.5 mg) and pitavastatin (1 or 2 mg) in 134 dyslipidemic patients with concurrent chronic kidney disease (CKD; rosuvastatin group, n=68; pitavastatin group, n=66). Lipid parameters [i.e., low density lipoprotein cholesterol (LDL-C), etc.], renal function parameters [i.e., estimated glomerular filtration rate (eGFR), etc.], glycated hemoglobin (HbA1c), and high-sensitivity C-reactive protein (hs-CRP) were measured at enrollment (baseline), month 6, and month 12.

RESULTS: The mean daily dose of rosuvastatin and pitavastatin was 2.5 mg and 1.4 mg, respectively. All lipid parameters were significantly more improved in the rosuvastatin group. eGFR improved from baseline in the rosuvastatin group ($p < 0.0001$) and showed no tendency to worsen in the pitavastatin group ($p=0.2232$). In multiple regression analysis (n=134), it was significantly associated with a percent change in total cholesterol (beta=0.2296; $p=0.0112$), smoking (beta=0.1927; $p=0.0224$), and HbA1c (beta=-0.1606; $p=0.0585$). Hs-CRP was significantly improved in both groups. An analysis eliminating the influence of antidiabetic medication showed a significant difference between groups in the change of HbA1c at month 6 from baseline ($p=0.0016$). No subjects in either group had new onset of diabetes mellitus. The cost of statin medication required to reduce LDL-C by 10 mg/dL was significantly lower for 2.5 mg of rosuvastatin ($p=0.0116$).

CONCLUSIONS: Rosuvastatin 2.5 mg had superior lipid lowering and cost effectiveness in dyslipidemic patients with concurrent CKD.(UMIN ID: UMIN000005812).

Araujo, D. B., M. C. Bertolami, et al. (2010). "Pleiotropic effects with equivalent low-density lipoprotein cholesterol reduction: comparative study between simvastatin and simvastatin/ezetimibe coadministration." Journal of Cardiovascular Pharmacology **55**(1): 1-5.

BACKGROUND: Coadministration of any statin with ezetimibe is as effective as using high doses of the same statin in the reduction of low-density lipoprotein cholesterol (LDL-c). There may be other effects called pleiotropics. OBJECTIVE: To compare the effectiveness of 2 different treatments that obtain equivalent LDL-c reductions (80 mg of simvastatin, once a day and coadministration of 10 mg of simvastatin and 10 mg of ezetimibe, once a day) over endothelial function and inflammation. METHODS: Twenty-three randomized patients with hypercholesterolemia in a 2 x 2 crossover protocol were studied. Endothelial function was analyzed by ultrasound assessment of endothelial dependent flow-mediated vasodilation of the brachial artery, and inflammation was estimated by high-sensitivity C-reactive protein (hs-CRP). RESULTS: LDL-c reduction was similar between the 2 treatments with simvastatin/ezetimibe and with simvastatin ($P < 0.001$); no difference between treatments was found ($P = 0.968$). Both treatments improved significantly the endothelial function [3.61% with simvastatin/ezetimibe ($P = 0.003$) and 5.08% with simvastatin ($P < 0.001$)]; no difference was found between the 2

treatments (P = 0.291). hs-CRP had a 23% reduction with simvastatin/ezetimibe (P = 0.004) and a 30% reduction with simvastatin alone (P = 0.01), with no significant difference between the 2 treatments (P = 0.380). CONCLUSION: The 2 forms of treatment presented similar pleiotropic effects: improvement in endothelial function and decrease in hs-CRP levels.

Arimura, T., S.-i. Miura, et al. (2012). "Comparison of the efficacy and safety of statin and statin/ezetimibe therapy after coronary stent implantation in patients with stable angina." Journal of Cardiology 60(2): 111-118.

Little is known about the efficacy and safety of intensive lowering of low-density lipoprotein cholesterol (LDL-C) with statin/ezetimibe therapy after coronary stent implantation in patients with stable angina. Fifty patients with stable angina were randomly divided into an atorvastatin (10 mg/day) (A) group and an atorvastatin (10 mg/day)/ezetimibe (10 mg/day) (A+E) group after stent implantation. Follow-up coronary angiography was performed at 6-9 months after stenting. The A and A+E groups showed significant reductions in LDL-C. The levels of LDL-C in the A+E group were significantly lower than those in the A group at follow-up, whereas there were no differences in major adverse cardiac events, in-stent restenosis, or in-stent % diameter stenosis (DS) between the groups. Only the A+E group showed a significant decrease in the levels of highly sensitive C-reactive protein. In a sub-analysis, %DS in the non-target vessel significantly decreased in both groups. Moreover, %DS (=the value at baseline minus that at follow-up) in the A+E group was more closely associated with LDL-C levels at follow-up than that in the A group. There were no significant differences in adverse effects between the A and A+E groups. In conclusion, although statin/ezetimibe therapy was effective and safe for intensive lipid-lowering in patients with stable angina after successful coronary stent implantation, improvement in clinical outcomes with the combination therapy remains unclear.

Bando, Y., et al. (2016). "Switching from atorvastatin to rosuvastatin lowers small, dense low-density lipoprotein cholesterol levels in Japanese hypercholesterolemic patients with type 2 diabetes mellitus." Diabetes Research & Clinical Practice **111**: 66-73.

AIMS: This open-label, randomized, parallel-group comparative study compared the efficacy of rosuvastatin (5mg/day) and atorvastatin (10mg/day) for reduction of small dense low-density lipoprotein cholesterol (sd LDL-C) levels in Japanese patients with type 2 diabetes mellitus (T2DM).

METHODS: Patients with T2DM and hypercholesterolemia with detectable sd LDL-C after receiving 10mg/day atorvastatin for > 24 weeks were randomly assigned to receive rosuvastatin (5mg/day; switched treatment) or atorvastatin (10mg/day; continued treatment) for 12 weeks. The primary endpoints were changes in sd LDL-C levels and sd LDL-C/total LDL-C ratio evaluated using the LipoPhor AS() system.

RESULTS: There were no significant percent changes from baseline for LDL-C levels between the switched (n=55) and the continued treatment group (n=56). However, the former group exhibited a statistically significant reduction from baseline of sd LDL-C levels, sd LDL-C/total LDL-C ratio compared with the latter group (-3.8 mg/dL vs. -1.4 mg/dL, p=0.014; -2.3% vs. -0.6%, p=0.004, respectively). Multiple regression analysis among all

subjects revealed that independent factors contributing to the reduction in sd LDL-C levels were a change in LDL-C (p=0.003) and triglyceride (TG) levels (p=0.006), treatment group (the switched group=1, the continued group=0; standard coefficient=-1.2, p=0.034) and baseline glycated hemoglobin A1c (HbA1c) (p=0.045), respectively.
CONCLUSION: Switching from 10mg atorvastatin to 5mg rosuvastatin may be a useful therapeutic option to reduce sd LDL-C levels in Japanese hypercholesterolemic patients with T2DM.

Bohula, E. A., et al. (2015). "Achievement of dual low-density lipoprotein cholesterol and high-sensitivity C-reactive protein targets more frequent with the addition of ezetimibe to simvastatin and associated with better outcomes in IMPROVE-IT." Circulation **132**(13): 1224-1233.
BACKGROUND: Statins lower low-density lipoprotein cholesterol (LDL-C) and high-sensitivity C-reactive protein (hs-CRP); addition of ezetimibe to statins further reduces LDL-C and hs-CRP. An analysis of the relationship between achieved LDL-C and hs-CRP targets and outcomes for simvastatin and ezetimibe/simvastatin was prespecified in Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT).
METHODS AND RESULTS: The IMPROVE-IT trial randomly assigned 18 144 patients stabilized after acute coronary syndrome to simvastatin or ezetimibe/simvastatin. LDL-C and hs-CRP were measured at baseline and 1 month after randomization. Outcomes were assessed in those achieving one or both of the prespecified targets of LDL-C<70 mg/dL and hs-CRP<2 mg/L versus achieving neither target, adjusting for differences in baseline characteristics. An exploratory analysis examined targets of LDL-C<50 mg/dL and hs-CRP<1 mg/L. Patients meeting both targets at baseline, with no 1-month values, or with end points before 1 month were excluded. Of 15 179 patients, 39% achieved the dual LDL-C (<70 mg/dL) and hs-CRP (<2 mg/L) targets at 1 month, 14% met neither target, 14% met only the hs-CRP target, and 33% met only the LDL-C target. Those achieving dual targets had lower primary end point rates than those meeting neither target (cardiovascular death, major coronary event, or stroke; 38.9% versus 28.0%; adjusted hazard ratio, 0.73; 0.66-0.81; P<0.001). More patients treated with ezetimibe/simvastatin met dual targets than those treated with simvastatin alone (50% versus 29%, P<0.001). The association of dual-target attainment with improved outcomes was similar irrespective of treatment assignment (P-interaction=0.65). Similar findings were observed using the exploratory targets.
CONCLUSIONS: Significantly more patients treated with ezetimibe/simvastatin met prespecified and exploratory dual LDL-C and hs-CRP targets than patients treated with simvastatin alone. Reaching both LDL-C and hs-CRP targets was associated with improved outcomes after multivariable adjustment.
CLINICAL TRIAL REGISTRATION: URL: http://www.clinicaltrials.gov; Unique identifier: NCT00202878.

Constance, C., et al. (2014). "Atorvastatin 10 mg plus ezetimibe versus titration to atorvastatin 40 mg: attainment of European and Canadian guideline lipid targets in high-risk subjects >65 years." Lipids in Health & Disease **13**: 13.
BACKGROUND: Few clinical studies have focused on the efficacy of lipid-lowering

therapies in patients >65 years.
METHODS: After stabilization on atorvastatin 10 mg, hypercholesterolemic subjects >65 years at high/very high risk for CHD and not at LDL-C <1.81 mmol/L (with atherosclerotic vascular disease [AVD]) or <2.59 mmol/L (without AVD) were randomized to ezetimibe 10 mg plus atorvastatin 10 mg or uptitration to atorvastatin 20 mg (6 weeks) followed by uptitration to 40 mg (additional 6 weeks). A post-hoc analysis compared between-group differences in percent attainment of individual and combined LDL-C, non-HDL-C and Apo B targets based on recommendations from 2012 European and Canadian Cardiovascular Society (CCS) guidelines for dyslipidemia treatment.
RESULTS: Atorvastatin 10 mg plus ezetimibe produced significantly greater attainment of LDL-C, non-HDL-C, and Apo B individual and dual/triple targets vs atorvastatin 20 mg for the entire cohort and very high-risk groups at 6 weeks. After 12 weeks, very high-risk subjects maintained significantly greater achievement of LDL-C <1.8 mmol/L (47% vs 35%), non-HDL-C <2.6 mmol/L (63% vs 53%) and Apo B <0.8 g/L (47% vs 38%) single targets and dual/triple targets with atorvastatin 10 mg plus ezetimibe vs atorvastatin 40 mg, while attainment of European target for high-risk subjects was generally similar for both treatments. Achievement of Canadian targets was significantly greater with combination therapy vs atorvastatin 20 mg (6 weeks) or atorvastatin 40 mg (12 weeks).
CONCLUSIONS: Atorvastatin 10 mg plus ezetimibe provided more effective treatment than uptitration to atorvastatin 20/40 mg for attainment of most European and Canadian guideline-recommended lipid targets in older at-risk patients.
TRIAL REGISTRATION: ClinicalTrials.gov identifier NCT00418834.

de Zeeuw, D., et al. (2015). "Renal effects of atorvastatin and rosuvastatin in patients with diabetes who have progressive renal disease (PLANET I): a randomised clinical trial." The Lancet Diabetes & Endocrinology **3**(3): 181-190.
BACKGROUND: The role of lipid-lowering treatments in renoprotection for patients with diabetes is debated. We studied the renal effects of two statins in patients with diabetes who had proteinuria.
METHODS: PLANET I was a randomised, double-blind, parallel-group trial done in 147 research centres in Argentina, Brazil, Bulgaria, Canada, Denmark, France, Hungary, Italy, Mexico, Romania, and the USA. We enrolled patients with type 1 or type 2 diabetes aged 18 years or older with proteinuria (urine protein:creatinine ratio [UPCR] 500-5000 mg/g) and taking stable angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or both. We randomly assigned participants to atorvastatin 80 mg, rosuvastatin 10 mg, or rosuvastatin 40 mg for 52 weeks. The primary endpoint was change from baseline to week 52 of mean UPCR in each treatment group. The study is registered with ClinicalTrials.gov, number NCT00296374.
FINDINGS: We enrolled 353 patients: 118 were assigned to rosuvastatin 10 mg, 124 to rosuvastatin 40 mg, and 111 to atorvastatin 80 mg; of these, 325 were included in the intention-to-treat population. UPCR baseline:week 52 ratio was 087 (95% CI 077-099; p=0033) with atorvastatin 80 mg, 102 (088-118; p=083) with rosuvastatin 10 mg, and 096 (083-111; p=053) with rosuvastatin 40 mg. In a post-hoc analysis to compare statins, we combined data from PLANET I with those from PLANET II (a similar randomised parallel study of 237 patients with proteinuria but without diabetes; registered with

ClinicalTrials.gov, NCT00296400). In this analysis, atorvastatin 80 mg lowered UPCR significantly more than did rosuvastatin 10 mg (-156%, 95% CI -283 to -05; p=0043) and rosuvastatin 40 mg (-182%, -302 to -42; p=0013). Adverse events occurred in 69 (60%) of 116 patients in the rosuvastatin 10 mg group versus 79 (64%) of 123 patients in the rosuvastatin 40 mg group versus 63 (57%) of 110 patients in the atorvastatin 80 mg group; renal events occurred in nine (78%) versus 12 (98%) versus five (45%).

INTERPRETATION: Despite high-dose rosuvastatin lowering plasma lipid concentrations to a greater extent than did high-dose atorvastatin, atorvastatin seems to have more renoprotective effects for the studied chronic kidney disease population.

FUNDING: AstraZeneca.

Eriksson, M., D. Budinski, et al. (2011a). "Comparative efficacy of pitavastatin and simvastatin in high-risk patients: a randomized controlled trial." Advances in Therapy **28**(9): 811-823.

INTRODUCTION: Despite the proven efficacy of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) in lowering total and low-density lipoprotein cholesterol (LDL-C), many patients do not reach recommended lipid targets. This study compared pitavastatin, a new and highly effective statin, and simvastatin in patients at high risk of coronary heart disease (CHD). The primary objective was to demonstrate noninferiority of pitavastatin to simvastatin.

METHODS: The study was a phase 3, randomized, double-blind, double-dummy, parallel-group, active-controlled study conducted at 37 centers in five European countries. Following a dietary run-in period of 6-8 weeks, patients with primary hypercholesterolemia or combined dyslipidemia and at least two CHD risk factors were randomized 2:1 to receive pitavastatin 4 mg or simvastatin 40 mg once daily for 12 weeks. The primary efficacy variable was the change in LDL-C from baseline.

RESULTS: In total, 355 patients were randomized, 236 to pitavastatin and 119 to simvastatin; 330 patients (223 and 107, respectively) completed the study. In the pitavastatin group, mean (+/- SD) reduction in LDL-C concentrations from baseline was -44.0 +/- 12.8% compared with -43.8 +/- 14.4% in the simvastatin group. The adjusted mean treatment difference (simvastatin--pitavastatin) was 0.31% (95% confidence interval -2.47, 3.09; P = 0.829), which was within the predefined noninferiority range. More than 80% of patients in each group reached recommended LDL-C targets. Pitavastatin provided a greater increase in high-density lipoprotein cholesterol (HDL-C; 6.8% vs 4.5%; P = 0.083) and a significantly greater decrease in triglycerides (-19.8% vs -14.8%; P = 0.044) than simvastatin. Both treatments were well tolerated.

CONCLUSION: Pitavastatin 4 mg is as effective as simvastatin 40 mg in lowering LDL-C in dyslipidemic patients at high risk of CHD, with additional effects on HDL-C and triglycerides. Therefore, pitavastatin may be appropriate for the management of dyslipidemic patients at high cardiovascular risk.

Florentin, M., E. N. Liberopoulos, et al. (2011). "The effect of simvastatin alone versus simvastatin plus ezetimibe on the concentration of small dense low-density lipoprotein cholesterol in subjects with primary hypercholesterolemia." Current Medical Research & Opinion 27(3): 685-692.

OBJECTIVE: To compare the effects of simvastatin alone versus simvastatin plus ezetimibe on small dense low-density lipoprotein cholesterol (sdLDL-C) concentration in

subjects with primary hypercholesterolemia.
RESEARCH DESIGN AND METHODS: Patients with LDL-C levels above those recommended by the National Cholesterol Education Program Adult Treatment Panel III were randomized to open-label simvastatin 40mg (n=50) or simvastatin/ezetimibe 10/10mg as a fixed combination (n=50) daily. LDL particle size (estimated by electrophoresis), sdLDL-C levels, and lipid profile were blindly assessed at baseline and 3 months.
CLINICAL TRIAL REGISTRATION: clinicaltrials.gov NCT00932620.
RESULTS: Both simvastatin 40mg and simvastatin/ezetimibe 10/10mg decreased total cholesterol (-31% and -36%, respectively), LDL-C (-43% and -49%, respectively), triglycerides (-17% and -19%, respectively), non-high-density lipoprotein cholesterol (non-HDL-C; -40% and -46%, respectively), large LDL-C (-40 and -44%, respectively) and sdLDL-C levels (-42% and -46%, respectively, all p<0.000 vs baseline) and increased LDL particle size (+0.5% and +0.7%, respectively, both p<0.05 vs baseline). The changes in total cholesterol, LDL-C and non-HDL-C were greater in the simvastatin/ezetimibe group (all p<0.05). Changes in triglycerides, large LDL-C, sdLDL-C levels and LDL particle size were similar in the two groups. In multivariate analysis, baseline sdLDL-C and triglyceride levels, but not the choice of treatment, were significantly and independently correlated with the changes in sdLDL-C levels.
CONCLUSION: The combination of simvastatin 10mg plus ezetimibe 10mg is similarly effective to simvastatin 40mg in improving sdLDL-C concentration and LDL particle size in subjects with primary hypercholesterolemia.

Foody, J. M., W. V. Brown, et al. (2010). "Safety and efficacy of ezetimibe/simvastatin combination versus atorvastatin alone in adults >=65 years of age with hypercholesterolemia and with or at moderately high/high risk for coronary heart disease (the VYTELD study)." American Journal of Cardiology **106**(9): 1255-63.

Higher than 80% of coronary heart disease-related mortality occurs in patients >=65 years of age. Guidelines recommend low-density lipoprotein (LDL) cholesterol targets for these at-risk patients; however, few clinical studies have evaluated lipid-lowering strategies specifically in older adults. This multicenter, 12-week, randomized, double-blind, parallel-group trial evaluated the efficacy and safety of the usual starting dose of ezetimibe/simvastatin (10/20 mg) versus atorvastatin 10 or 20 mg and the next higher dose of ezetimibe/simvastatin (10/40 mg) versus atorvastatin 40 mg in 1,289 hypercholesterolemic patients >=65 years of age with or without cardiovascular disease. Patients randomized to ezetimibe/simvastatin had greater percent decreases in LDL cholesterol (-54.2% for 10/20 mg vs -39.5% and -46.6% for atorvastatin 10 and 20 mg, respectively; -59.1% for 10/40 mg vs -50.8% for atorvastatin 40 mg; p <0.001 for all comparisons) and the number attaining LDL cholesterol <70 mg/dl (51.3% for 10/20 mg, 68.2% for 10/40 mg) and <100 mg/dl (83.6% for 10/20 mg; 90.3% for 10/40 mg) was significantly larger compared to those receiving atorvastatin for all prespecified dose comparisons (p <0.05 to <0.001). A significantly larger percentage of high-risk patients achieved LDL cholesterol <70 mg/dl on ezetimibe/simvastatin 10/20 mg (54.3%) versus atorvastatin 10 mg (10.9%, p <0.001) or 20 mg (28.9%, p <0.001) and ezetimibe/simvastatin 10/40 mg (69.2%) versus atorvastatin 40 mg (38.2%, p <0.001), and a significantly larger percentage of intermediate-risk patients achieved LDL

cholesterol <100 mg/dl on ezetimibe/simvastatin 10/20 mg (82.1%) versus atorvastatin 10 mg (59.3%, p <0.05). Improvements in non-high-density lipoprotein cholesterol, total cholesterol, apolipoprotein B, and lipoprotein ratios were significantly greater with ezetimibe/simvastatin than atorvastatin for all comparisons (p <0.01 to <0.001). High-density lipoprotein cholesterol and triglyceride results were variable. All treatments were generally well tolerated. In conclusion, ezetimibe/simvastatin provided significantly greater improvements in key lipid parameters and higher attainment of LDL cholesterol targets than atorvastatin, with comparable tolerability.

Gibson, C. M., Y. B. Pride, et al. (2009). "Effect of intensive statin therapy on clinical outcomes among patients undergoing percutaneous coronary intervention for acute coronary syndrome. PCI-PROVE IT: A PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22) Substudy." Journal of the American College of Cardiology 54(24): 2290-5.

OBJECTIVES: The goal of this analysis was to determine whether intensive statin therapy, compared with moderate-dose statin therapy, leads to a reduction in major adverse cardiovascular events (MACE) among patients undergoing percutaneous coronary intervention (PCI) for acute coronary syndrome (ACS). BACKGROUND: When compared with moderate-dose statins, intensive statin therapy reduces MACE among patients with ACS. The role of intensive statin therapy specifically among patients who undergo PCI for ACS is unknown. METHODS: Outcomes were compared in 2,868 patients who underwent PCI for ACS just prior to enrollment in the PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22) trial, which randomized patients to either atorvastatin 80 mg or pravastatin 40 mg daily. The incidence of the primary composite end point of all-cause mortality, myocardial infarction, unstable angina leading to hospitalization, and revascularization after 30 days and stroke was evaluated, as was the incidence of target vessel revascularization (TVR) and non-TVR during follow-up. RESULTS: Treatment with 80 mg atorvastatin reduced the incidence of the composite end point (21.5% vs 26.5%, hazard ratio: 0.78, 95% confidence interval: 0.67 to 0.91, p=0.002) and lowered the incidence of both TVR (11.4% vs 15.4%, p=0.001) and non-TVR (8.0% vs 10.5%, p=0.017) compared with 40 mg pravastatin. After adjusting for on-treatment serum low-density lipoprotein cholesterol and C-reactive protein concentrations, the odds of TVR with high-dose statin therapy remained significant (odds ratio: 0.74, p=0.015) while the odds of non-TVR did not (odds ratio: 0.92, p=0.55). CONCLUSIONS: Among patients with ACS who undergo PCI, intensive statin therapy reduces MACE compared with moderate-dose statin therapy. The reduction in the incidence of TVR was independent of low-density lipoprotein cholesterol and C-reactive protein lowering and may therefore be due, at least in part, to a pleiotropic effect of high-dose statin therapy. (PROVE IT-TIMI 22; NCT00382460).

Gumprecht, J., M. Gosho, et al. (2011). "Comparative long-term efficacy and tolerability of pitavastatin 4 mg and atorvastatin 20-40 mg in patients with type 2 diabetes mellitus and combined (mixed) dyslipidaemia." Diabetes, Obesity & Metabolism 13(11): 1047-1055.

AIM: To compare the long-term efficacy and safety of pitavastatin with atorvastatin in patients with type 2 diabetes and combined (mixed) dyslipidaemia.

METHODS: Randomised, double-blind, active-controlled, multinational non-inferiority study. Patients were randomised 2 : 1 to pitavastatin 4 mg (n = 279) or atorvastatin 20 mg (n = 139) daily for 12 weeks. Patients completing the core study could continue on pitavastatin 4 mg (n = 141) or atorvastatin 20 mg (n = 64) [40 mg (n = 7) if lipid targets not reached by week 8] for a further 44 weeks (extension study). The primary efficacy variable was the change in low-density lipoprotein cholesterol (LDL-C).

RESULTS: Reductions in LDL-C were not significantly different at week 12 between the pitavastatin (-41%) and atorvastatin (-43%) groups. Attainment of National Cholesterol Education Program and European Atherosclerosis Society targets for LDL-C and non-high-density lipoprotein cholesterol (non-HDL-C) was similarly high for both treatment groups. Changes in secondary lipid variables (e.g. HDL-C, apolipoprotein B and triglycerides) were similar between treatments. Post hoc analysis showed that adjusted mean treatment differences for pitavastatin vs atorvastatin were within the non-inferiority margin at weeks 16 (+0.11%; 95% confidence interval (CI), -5.23 to 5.44) and 44 (-0.02%; 95% CI, -5.46 to 5.41) of the extension study. Both treatments were well tolerated; atorvastatin increased fasting blood glucose from baseline (+7.2%; $p < 0.05$), whereas pitavastatin had no significant effect (+2.1%).

CONCLUSIONS: Reductions in LDL-C and changes in other lipids were not significantly different in patients treated with pitavastatin 4 mg or atorvastatin 20 or 40 mg. Pitavastatin may, however, have a more favourable effect on the glycaemic status. 2011 Blackwell Publishing Ltd.

Hall, A. S., B. M. Jackson, et al. (2009). "A randomized, controlled trial of simvastatin versus rosuvastatin in patients with acute myocardial infarction: the Secondary Prevention of Acute Coronary Events--Reduction of Cholesterol to Key European Targets Trial." European Journal of Cardiovascular Prevention & Rehabilitation **16**(6): 712-21.

AIMS: We sought to evaluate reports that rosuvastatin 10 mg is a more efficacious treatment of hyperlipidaemia than is simvastatin 40 mg, hoping to assess this issue in the previously unstudied context of acute myocardial infarction. METHODS AND RESULTS: The Secondary Prevention of Acute Coronary Events - Reduction of Cholesterol to Key European Targets (SPACE ROCKET) Trial was an investigator-led, open-label, blinded-endpoint, multicentre, randomized, controlled trial assessing the proportion of patients, at 3 months, achieving European Society of Cardiology 2003 (ESC-03) lipid targets of total cholesterol (TC) less than 4.5 mmol/l (174 mg/dl) or low-density lipoprotein cholesterol (LDLc) less than 2.5 mmol/l (97 mg/dl). Of 1263 patients randomized, 77.6% simvastatin versus 79.9% rosuvastatin achieved ESC-03 targets [odds ratio (OR): 1.16; 95% confidence interval (CI): 0.88-1.53; P = 0.29]. There were statistically significant differences for simvastatin versus rosuvastatin, respectively, for mean LDLc 2.03 mmol/l (78 mg/dl) versus 1.94 mmol/l (75 mg/dl; P = 0.009) and also mean TC 3.88 mmol/l (150 mg/dl) versus 3.75 mmol/l (145 mg/dl; P = 0.005). A post-hoc analysis showed higher achievement of the new ESC, American Heart Association and American College of Cardiology optimal lipid target of LDLc less than 1.81 mmol/l (70 mg/dl) with rosuvastatin (45.0%) compared with simvastatin (37.8%; OR: 1.37; 95% CI: 1.09-1.72; P = 0.007). The proportion of patients achieving the Fourth Joint Task Force European Guidelines (2007) of TC less than 4.0 mmol/l (155 mg/dl) and LDLc less than 2.0 mmol/l (77 mg/dl) was 38.7% for simvastatin 40 mg and 47.7% for rosuvastatin

10 mg (OR: 1.48; 95% CI: 1.18-1.86; P = 0.001). CONCLUSION: We observed no superiority of either treatment for the ESC-03 lipid targets. Rosuvastatin 10 mg lowered mean cholesterol more effectively than simvastatin and achieved better results for the latest, more stringent, ESC target.

Han, K. H., S. W. Rha, et al. (2012). "Evaluation of short-term safety and efficacy of HMG-CoA reductase inhibitors in hypercholesterolemic patients with elevated serum alanine transaminase concentrations: PITCH study (PITavastatin versus atorvastatin to evaluate the effect on patients with hypercholesterolemia and mild to moderate hepatic damage)." Journal of Clinical Lipidology 6(4): 340-351.

BACKGROUND: We evaluated the safety and efficacy of the 3-hydroxyl-3-methylglutaryl coenzyme A reductase inhibitors atorvastatin and pitavastatin in patients with mild-to-moderate increased levels of hepatic enzymes.

METHODS AND RESULTS: In this 12-week, prospective, randomized, open-label, active drug-controlled, and dose-titration study, 189 subjects with elevated low-density lipoprotein cholesterol (>=3.36 mmol/L) and alanine transaminase (ALT; x1.25>= and <=x2.5 ULN; 50-100 IU/L) concentrations, but nonalcoholic and serologically negative for viral hepatitis markers at screening, were randomized to 12 weeks of treatment with pitavastatin 2-4 mg/day (PITA, n= 97) or atorvastatin 10-20 mg/day (ATOR, n= 92). Pitavastatin and atorvastatin equally reduced low-density lipoprotein cholesterol concentrations (-34.6 +/- 16.0% and -38.1 +/- 16.2%, respectively, P < .0001 each by analysis of variance). Seven (n= 4 PITA, n= 3 ATOR) and 10 (n= 5 PITA, n= 5 ATOR) patients experienced episodes of ALT >100 IU/L at weeks 4 and 12, respectively, with one patient in each group excluded because of severe ALT elevation >3x ULN (>120 IU/L) at week 4. The 135 patients with persistently increased ALT concentrations at screening and randomization showed significant reductions in ALT after 12 weeks of treatment with PITA (n= 68, -8.4%) or ATOR (n= 67, -8.9%; P < .05, analysis of variance). Serial nonenhanced computed tomography in 38 subjects (n= 18 PITA, n= 20 ATOR) showed that both statins reduced the severity of hepatic steatosis, especially in subjects with clear hepatic steatosis at baseline (n= 9 PITA, n= 10 ATOR). Statin treatment of another 38 subjects with spontaneous normalization of ALT at randomization had little effect on ALT levels but did not induce severe ALT elevation (>100 IU/L).

CONCLUSIONS: Conventional doses of pitavastatin and atorvastatin effectively and safely reduce elevated hepatic enzyme concentrations. Copyright 2012 National Lipid Association. Published by Elsevier Inc. All rights reserved.

Hongo, M., S. Kumazaki, et al. (2011). "Low-dose rosuvastatin improves arterial stiffness in high-risk Japanese patients with dyslipdemia in a primary prevention group." Circulation Journal 75(11): 2660-2667.

BACKGROUND: The treatment effects of rosuvastatin on arterial stiffness were assessed and compared to those of fluvastatin in high-risk Japanese patients with dyslipidemia in a primary prevention group.

METHODS AND RESULTS: Patients were randomly assigned to either 2.5-5 mg/day of rosuvastatin (Group A) or 20-40 mg/day of fluvastatin (Group B) and followed up for 12 months. In Group A (n=38), there was a progressive reduction in brachial-ankle pulse

wave velocity (baPWV) along with a decrease in the low-density lipoprotein cholesterol/high-density lipoprotein cholesterol (L/H) ratio and high-sensitivity C-reactive protein (hsCRP), and the change in baPWV correlated significantly with that of the L/H ratio and that of hsCRP after rosuvastatin treatment. In Group B (n=37), although fluvastatin achieved a significant improvement in baPWV, L/H ratio, and hsCRP, baPWV was significantly greater than that in Group A and showed a significant correlation with that of hsCRP alone after fluvastatin treatment. In a subgroup of patients (n=26), switching from fluvastatin to rosuvastatin further improved baPWV and the L/H ratio without altering hsCRP after 12 months.

CONCLUSIONS: Low-dose rosuvastatin would be more effective than fluvastatin in improving arterial stiffness in high-risk Japanese patients with dyslipidemia. The results suggest that improvement in arterial stiffness by rosuvastatin mainly depends on its strong lipid-lowering effects, whereas that by fluvastatin is strongly dependent on the pleiotropic effects, especially an anti-inflammatory action.

Im, E., et al. (2017). "High-intensity Statin Treatments in Clinically Stable Patients on Aspirin Monotherapy 12 Months After Drug-eluting Stent Implantation: a Randomized Study." Revista Espanola de Cardiologia(pagination).

Introduction and objectives: Current guidelines on the treatment of blood cholesterol recommend continuous maintenance of high-intensity statin treatment in drug-eluting stent (DES)-treated patients. However, high-intensity statin treatment is frequently underused in clinical practice after stabilization of DES-treated patients. Currently, the impact of continuous high-intensity statin treatment on the incidence of late adverse events in these patients is unknown. We investigated whether high-intensity statin treatment reduces late adverse events in clinically stable patients on aspirin monotherapy 12 months after DES implantation. Methods: Clinically stable patients who underwent DES implantation 12 months previously and received aspirin monotherapy were randomly assigned to receive either high-intensity (40. mg atorvastatin, n = 1000) or low-intensity (20. mg pravastatin, n = 1000) statin treatment. The primary endpoint was adverse clinical events at 12-month follow-up (a composite of all death, myocardial infarction, revascularization, stent thrombosis, stroke, renal deterioration, intervention for peripheral artery disease, and admission for cardiac events). Results: The primary endpoint at 12-month follow-up occurred in 25 patients (2.5%) receiving high-intensity statin treatment and in 40 patients (4.1%) receiving low-intensity statin treatment (HR, 0.58; 95%. CI, 0.36-0.92; P = .018). This difference was mainly driven by a lower rate of cardiac death (0 vs 0.4%, P = .025) and nontarget vessel myocardial infarction (0.1 vs 0.7%, P = .033) in the high-intensity statin treatment group. Conclusions: Among clinically stable DES-treated patients on aspirin monotherapy, high-intensity statin treatment significantly reduced late adverse events compared with low-intensity statin treatment.Clinical trial registration: URL: http://www.clinicaltrials.gov. Unique identifier: NCT01557075. Full English text available from: www.revespcardiol.org/en

Izawa, A., et al. (2015). "Assessment of lipophilic vs. hydrophilic statin therapy in acute myocardial infarction - ALPS-AMI study." Circulation Journal **79**(1): 161-168.

BACKGROUND: Statins reduce the incidence of cardiovascular events, but no randomized trial has investigated the best statins for secondary prevention. We compared the efficacy of hydrophilic pravastatin with that of lipophilic atorvastatin in patients with acute myocardial infarction (AMI).

METHODS AND RESULTS: A prospective, multicenter study enrolled 508 patients (410 men; mean age, 66.0 +/- 11.6 years) with AMI who were randomly assigned to atorvastatin (n=255) or pravastatin (n=253). The target control level of low-density lipoprotein cholesterol (LDL-C) was <100 mg/dl, and patients were followed for 2 years. The primary endpoint was the composite of death due to any cause, non-fatal myocardial infarction, non-fatal stroke, unstable angina or congestive heart failure requiring hospital admission, or any type of coronary revascularization. The primary endpoint occurred in 77 patients (30.4%) and in 80 patients (31.4%) in the pravastatin and atorvastatin groups, respectively (hazard ratio, 1.181; 95% confidence interval: 0.862-1.619; P=0.299), whereas greater reductions in serum total cholesterol and LDL-C were achieved in the atorvastatin group (P<0.001 for each). Changes in hemoglobin A1c, brain natriuretic peptide, and creatinine were not significant between the 2 regimens, and safety and treatment adherence were similar.

CONCLUSIONS: On 2-year comparison of hydrophilic and lipophilic statins there was no significant difference in prevention of secondary cardiovascular outcome.

Japaridze, L. and M. Sadunishvili (2017). "The short-term effect of atorvastatin plus ezetimibe therapy versus atorvastatin monotherapy on clinical outcome in acute coronary syndrome patients by gender." Kardiologia Polska **75**(8): 770-778.

Background: Atorvastatin reduces low-density lipoprotein cholesterol (LDL-C) levels and the risk of cardiovascular events, but whether the addition of ezetimibe (EZE), a non-statin drug that reduces intestinal cholesterol absorption, can reduce the rate of cardiovascular events further, and if there any sex differences, is not known. Aim: To evaluate the effects of atorvastatin and EZE combination in acute coronary syndrome (ACS) patients on the incidence of composite endpoint in short-term follow-up and to assess differences according their gender. Methods: We conducted a 16-week, single-centre, prospective, randomised, open-label clinical trial involving 323 patients who had been hospitalised for an ACS within the preceding 14 days. They received atorvastatin 20 mg for 28 days, and after that 292 patients who had LDL-C levels >= 1.81 mmol/L were randomised to EZE 10 mg/day co-administered with atorvastatin therapy (EZE + statin) or double their current atorvastatin dose. The primary endpoint was a composite of cardiovascular death, nonfatal myocardial infarction, unstable angina requiring rehospitalisation, coronary revascularisation (>= 30 days after randomisation), or nonfatal stroke. Results: The Kaplan-Meier event-free survival rate at 16 weeks was 88.1% in the EZE + statin group patients and 77.0% in the atorvastatin monotherapy group (absolute risk reduction: 11.1 percentage points; hazard ratio: 2.099; 95% confidence interval: 1.165-3.781; p = 0.014). The log rank test indicated that there was not a statistically significant difference between male and female survival rates in both treatment groups (p = 0.897). Conclusions: The results of our study demonstrated that when added to statin therapy, EZE resulted in improved cardiovascular outcomes, and the response to atorvastatin and EZE combination was similar for both men and women. Copyright (C) Polskie Towarzystwo Kardiologiczne 2017.

Japaridze, L., et al. (2016). "Combination Therapy Effectiveness of Ezetimibe and Atorvastatin in Patients with Acute Coronary Syndrome." Georgian Medical News(252): 15-22.

Atorvastatin reduces low-density lipoprotein (LDL) cholesterol levels and the risk of cardiovascular events, but whether the addition of ezetimibe (EZE) , a nonstatin drug that reduces intestinal cholesterol absorption, can reduce the rate of cardiovascular events further is not known. We conducted a 16-week one-center, prospective, randomized, and open-label clinical trial, involving 323 patients who had been hospitalized for an acute coronary syndrome within the preceding 14 days. They were received atorvastatin 20 mg during 28 days and after that 292 patients, who had LDL cholesterol levels>=1.81 mmol/L, were randomized to ezetimibe 10 mg/day co-administered with atorvastatin therapy (EZE+Statin) or doubling their current atorvastatin dose. The primary end point was a composite of cardiovascular death, nonfatal myocardial infarction, unstable angina requiring rehospitalization, coronary revascularization (>=30 days after randomization), or nonfatal stroke. At 16 weeks, the mean LDL cholesterol level during the study was 1.60 mmol per liter in the atorvastatine-ezetimibe group, as compared with 1.91 mmol per liter in the atorvastatin-monotherapy group (p<0.001). The Kaplan-Meier survival rate at 16 weeks were 88 .1 % in the atorvastatin-ezetimibe group and 77.0 % in the atorvastatin monotherapy group (absolute risk reduction, 11.1 percentage points; hazard ratio, 2.099 ; 95% confidence interval, 1.165 to 3.781; p=0.014). Patients receiving ezetimibe and statin were more likely to achieve target LDL-C after 16 weeks compared to patients doubling their statin dose. When added to statin therapy, ezetimibe resulted in incremental lowering of LDL cholesterol levels and improved cardiovascular outcomes. Ezetimibe/statin combination therapy was well tolerated among this patients, without safety concerns.

Joshi, P. H., et al. (2017). "Greater remnant lipoprotein cholesterol reduction with pitavastatin compared to pravastatin in HIV-infected patients: the INTREPID trial." AIDS(pagination).

OBJECTIVE:: Cardiovascular disease (CVD) is a leading cause of morbidity and mortality in those with HIV. An emerging CVD risk factor is triglyceride-rich remnant lipoprotein cholesterol (RLP-C: the sum of intermediate-density lipoprotein and very low-density lipoprotein3 cholesterol). The effects of statin therapy on lipoprotein subfractions, including RLP-C, in HIV-dyslipidemia are unknown. METHODS:: This is a post-hoc analysis of the randomized INTREPID trial (NCT 01301066) comparing pitavastatin 4?mg daily vs. pravastatin 40?mg daily in subjects with HIV. We measured apolipoproteins AI and B (apoAI, apoB) and lipoprotein cholesterol subfractions separated by density gradient ultracentrifugation at baseline and 12?weeks. We compared changes in atherogenic subfractions over 12 weeks in INTREPID participants using analysis of covariance. RESULTS:: Lipoprotein subfraction data were available for 213 subjects (pitavastatin n?=?104, pravastatin n?=?109). Baseline characteristics were similar between treatment groups. Reductions in RLP-C were significantly greater in the pitavastatin group compared to pravastatin group (-11.6?mg/dL vs -8.5?mg/dL; p?0.01). Similarly, ratios of risk (apoB/apoAI, total cholesterol/high-density lipoprotein cholesterol [HDL-C]) showed greater reductions with pitavastatin (p?<?0.05). There were no differences in changes in HDL-C, HDL-C subfractions or lipoprotein(a)-cholesterol levels. CONCLUSIONS:: In patients with HIV, pitavastatin 4?mg/d lowered both RLP-C

and established apolipoprotein and lipid risk ratios more so than pravastatin 40?mg/d. The impact of RLP-C reduction on CVD in HIV dyslipidemic patients merits further study. Copyright (C) 2017 Wolters Kluwer Health, Inc.

Kakuda, H., et al. (2014). "Comparison of atorvastatin, pitavastatin and rosuvastatin for residual cardiovascular risk using non-fasting blood sampling." Scandinavian Journal of Clinical & Laboratory Investigation **74**(4): 285-295.

BACKGROUND: Low-density lipoprotein cholesterol (LDL-C) is a major cardiovascular risk. However, some patients show symptoms of coronary heart disease (CHD) even though their LDL-C is strictly controlled. Therefore, it is important to treat other risk factors.

METHODS: Some 129 outpatients with dyslipidemia who were treated with either atorvastatin 10 mg/day (ATO), pitavastatin 2 mg/day (PIT), or rosuvastatin 2.5 mg/day (ROS) were enrolled. After informed consent was obtained, these patients were switched to another statin. Lipid profiles and lipoprotein fraction by polyacrylamide gel electrophoresis (PAGE) were compared between before and after 3 months of treatment with non-fasting blood sample.

RESULTS: LDL-C did not show any significant changes after switching and was maintained around 2.59 mmol/L in all groups. High-density lipoprotein cholesterol (HDL-C) was significantly increased in group ATO->PIT (1.43->1.54 mmol/L, p = 0.0010) and ROS->PIT (1.46->1.57 mmol/L, p = 0.0004), and was significantly decreased in group PIT->ATO (1.44->1.36 mmol/L, p = 0.0290). Apolipoprotein A-I (Apo A-I) and preheparin lipoprotein lipase (LPL) mass showed similar changes in HDL-C. Changes in HDL-C showed a significant positive correlation with those in Apo A-I and preheparin LPL mass, and a little but significant negative correlation with changes in Lp(a) and intermediate density lipoprotein (IDL) fraction.

CONCLUSIONS: ATO, PIT, and ROS have comparable effect on LDL-C lowering. Changes in HDL-C were similar to those in Apo A-I and preheparin LPL mass, and PIT was the most effective treatment in increasing HDL-C, Apo A-I, and preheparin LPL mass.

Kasmas, S. H., et al. (2012). "Differences in synthesis and absorption of cholesterol of two effective lipid-lowering therapies." Brazilian Journal of Medical & Biological Research **45**(11): 1095-1101.

Effective statin therapy is associated with a marked reduction of cardiovascular events. However, the explanation for full benefits obtained for LDL cholesterol targets by combined lipid-lowering therapy is controversial. Our study compared the effects of two equally effective lipid-lowering strategies on markers of cholesterol synthesis and absorption. A prospective, open label, randomized, parallel design study, with blinded endpoints, included 116 subjects. We compared the effects of a 12-week treatment with 40 mg rosuvastatin or the combination of 40 mg simvastatin/10 mg ezetimibe on markers of cholesterol absorption (campesterol and beta-sitosterol), synthesis (desmosterol), and their ratios to cholesterol. Both therapies similarly decreased total and LDL cholesterol, triglycerides and apolipoprotein B, and increased apolipoprotein A1 ($P < 0.05$ vs baseline for all). Simvastatin/ezetimibe increased plasma desmosterol ($P = 0.012$ vs baseline), and decreased campesterol and beta-sitosterol ($P < 0.0001$ vs baseline for both), with higher desmosterol ($P = 0.007$) and lower campesterol and beta-sitosterol compared to rosuvastatin, ($P < 0.0001$, for both). In addition, rosuvastatin increased the

ratios of these markers to cholesterol (P < 0.002 vs baseline for all), whereas simvastatin/ezetimibe significantly decreased the campesterol/cholesterol ratio (P = 0.008 vs baseline) and tripled the desmosterol/cholesterol ratio (P < 0.0001 vs baseline). The campesterol/cholesterol and beta-sitosterol/cholesterol ratios were lower, whereas the desmosterol/cholesterol ratio was higher in patients receiving simvastatin/ezetimibe (P < 0.0001 vs rosuvastatin, for all). Pronounced differences in markers of cholesterol absorption and synthesis were observed between two equally effective lipid-lowering strategies.

Koksal, M., M. A. Eren, et al. (2011). "The effects of atorvastatin and rosuvastatin on oxidative stress in diabetic patients." European Journal of Internal Medicine 22(3): 249-253.

AIM: Diabetes is associated with abnormalities in lipid profile and increased oxidative stress. Statins are preferred agents in diabetic patients due to their antioxidant and LDL-C lowering effects. This study is designed to compare the effects of atorvastatin and rosuvastatin on low density lipoprotein cholesterol (LDL-C), lipid hydroperoxide (LOOH), total oxidant status (TOS) and total antioxidant capacity (TAC) in diabetic patients with hyperlipidemia.

MATERIALS AND METHODS: Sixty two patients who have type 2 diabetes mellitus with serum LDL levels more than 100mg/dL were randomly assigned to receive atorvastatin 20mg (n=31) or rosuvastatin 10mg (n=31). Blood tests were performed at the beginning of the study and after three months.

RESULTS: There were no statistically significant differences in the pre- and after treatment levels of the LDL-C between groups. TAC values were increased in both groups and statistically significant in the former group (p=0.007). There was no difference between the change percentages ((after treatment TAC-pretreatment TAC)/pretreatment level) of TAC between two treatment groups. The effects of two drugs on the other oxidative parameters were not significantly different.

CONCLUSION: Both atorvastatin and rosuvastatin may be helpful in reducing increased oxidative stress in diabetic patients with hyperlipidemia.

Kurogi, K., S. Sugiyama, et al. (2013). "Comparison of pitavastatin with atorvastatin in increasing HDL-cholesterol and adiponectin in patients with dyslipidemia and coronary artery disease: the COMPACT-CAD study." Journal of Cardiology **62**(2): 87-94.

BACKGROUND: Many large-scale clinical trials have confirmed that statins are effective in reducing low-density lipoprotein cholesterol (LDL-C) level, resulting in reducing cardiovascular events. Recent studies have focused on the effects of statins on high-density lipoprotein cholesterol (HDL-C). Here we compared the effects of two statins on lipid profile and other metabolic parameters.

METHODS: The study population included 129 patients with stable coronary artery disease, hypercholesterolemia, and hypo-HDL-cholesterolemia (HDL-C<50mg/dl). They were randomly allocated to treatment by pitavastatin 2-4 mg/day or atorvastatin 10-20mg/day and followed-up for 30 months. The primary endpoint was percent changes in HDL-C and adiponectin during the study. The secondary endpoints were percent and absolute changes in markers of glucose metabolism, serum lipids, and apolipoproteins.

RESULTS: The effects of 30-month treatment with pitavastatin on HDL-C were significantly greater than those of atorvastatin (%change: pitavastatin: 20.1 + 25.7%, atorvastatin: 6.3

+ 19.8%, p=0.01; absolute change: pitavastatin: 7.3 + 9.1mg/dl, atorvastatin: 2.3 + 8.0mg/dl, p=0.02). A similar trend was seen with regard to apolipoprotein-AI (ApoAI) (%change: pitavastatin: 20.8 + 19.3%, atorvastatin: 11.4 + 17.6%, p=0.03; absolute change: pitavastatin: 23.1 + 20.2mg/dl, atorvastatin: 12.1 + 19.4 mg/dl, p=0.02). Treatment with pitavastatin, but not atorvastatin, significantly increased adiponectin levels. Neither statin had a significant effect on hemoglobin A1c. No severe adverse events were registered during the study.
CONCLUSION: Long-term treatment with pitavastatin resulted in significantly greater increases in serum HDL-C and ApoAI levels without adverse effects on glucose metabolism, compared with atorvastatin. Copyright 2013. Published by Elsevier Ltd.

Lablanche, J. M., A. Leone, et al. (2010). "Comparison of the efficacy of rosuvastatin versus atorvastatin in reducing apolipoprotein B/apolipoprotein A-1 ratio in patients with acute coronary syndrome: results of the CENTAURUS study." Archives of cardiovascular diseases **103**(3): 160-9.
BACKGROUND: The mechanism underlying statin-induced event reduction in patients with acute coronary syndrome remains unclear. AIMS: To assess the efficacy of rosuvastatin 20mg versus atorvastatin 80 mg in reducing the apolipoprotein B/apolipoprotein A-1 (apoB/apoA-1) ratio at 3 months. Non-inferiority of rosuvastatin 20mg versus atorvastatin 80 mg in reducing low-density lipoprotein cholesterol at 1 and 3 months was also assessed. METHODS: Patients with non-ST-elevation acute coronary syndrome were enrolled into this randomized, double blind, parallel-group trial. RESULTS: In total, 753 patients (369, rosuvastatin 20mg; 384, atorvastatin 80 mg) were included in the intention-to-treat analysis; 478 patients (226, rosuvastatin 20mg; 252, atorvastatin 80 mg) were included in the per-protocol analysis. Rosuvastatin 20mg was more effective than atorvastatin 80 mg in decreasing apoB/apoA-1 ratio at 1 month (-44.4% vs -42.9%, p=0.02) but not at 3 months (both -44.4%, p=0.87). Low-density lipoprotein cholesterol decreased by approximately 50% after 1 and 3 months in both groups. Non-inferiority of rosuvastatin 20mg versus atorvastatin 80 mg was demonstrated at 1 month (difference, -0.3% [95% confidence interval, -2.7; +2.1]), but not at 3 months (+1.0% [-1.6; 3.5]) (intention-to-treat analysis). In the per-protocol analysis, non-inferiority of rosuvastatin 20mg was demonstrated at both 1 (-0.7% [-3.5; 2.0]) and 3 (-0.5% [-3.5; 2.5]) months. CONCLUSION: In patients with non-ST-elevation acute coronary syndrome, rosuvastatin 20mg decreased apoB/apoA-1 ratio at 1 month more than atorvastatin 80 mg. No difference could be shown at 3 months; thus, the primary endpoint was not met.

Lee, C. W., S.-J. Kang, et al. (2012). "Comparison of effects of atorvastatin (20 mg) versus rosuvastatin (10 mg) therapy on mild coronary atherosclerotic plaques (from the ARTMAP trial)." American Journal of Cardiology 109(12): 1700-1704.
High-dose rosuvastatin induces regression of coronary atherosclerosis, but it remains uncertain whether usual-dose statin has similar effects. We compared the effects of atorvastatin 20 mg/day versus rosuvastatin 10 mg/day on mild coronary atherosclerotic plaques (20% to 50% luminal narrowing and lesion length >10 mm) using intravascular ultrasound (IVUS). Three hundred fifty statin-naive patients with mild coronary atherosclerotic plaques were randomized to receive atorvastatin 20 mg/day or

rosuvastatin 10 mg/day. IVUS examinations were performed at baseline and 6-month follow-up. Primary end point was percent change in total atheroma volume (TAV) defined as (TAV at 6 months - TAV at baseline)/(TAV at baseline) x 100. Evaluable IVUS was obtained for 271 patients (atorvastatin in 143, rosuvastatin in 128). Clinical characteristics, lipid levels, and IVUS measurements at baseline were similar between the 2 groups. At 6-month follow-up, percent change in TAV was significantly less in the atorvastatin group than in the rosuvastatin group (-3.9 +/- 11.9% vs -7.4 +/- 10.6%, respectively, p = 0.018). In contrast, change in percent atheroma volume was not different between the 2 groups (-0.3 +/- 4.2 vs -1.1 +/- 3.5, respectively, p = 0.157). Compared to baseline, TAV and TAV at the most diseased 10-mm subsegment were significantly decreased in the 2 groups (p <0.001). Changes in lipid profiles at 6-month follow-up were similar between the 2 groups. In conclusion, usual doses of atorvastatin and rosuvastatin induced significant regression of coronary atherosclerosis in statin-naive patients, with a greater decrease in favor of rosuvastatin. Copyright 2012 Elsevier Inc. All rights reserved.

Lee, J.-H., H.-J. Kang, et al. (2013). "Effects of ezetimibe/simvastatin 10/20 mg vs atorvastatin 20 mg on apolipoprotein B/apolipoprotein A1 in Korean patients with type 2 diabetes mellitus: results of a randomized controlled trial." American Journal of Cardiovascular Drugs **13**(5): 343-351.

BACKGROUND: Although the efficacy of ezetimibe/simvastatin and atorvastatin on traditional lipid parameters has been studied extensively, the apolipoprotein B/apolipoprotein A1 (ApoB/ApoA1) ratio, which has a better predictive value for cardiovascular events, has not previously been used as a primary endpoint in these two treatment groups.

OBJECTIVE: Our objective was to compare the efficacy and safety of ezetimibe/simvastatin 10/20 mg versus atorvastatin 20 mg once daily in Korean patients with type 2 diabetes mellitus.

STUDY DESIGN: This study was an open-label, randomized, controlled study. Type 2 diabetes patients with high levels of low-density lipoprotein (LDL) cholesterol (>100 mg/dL) were randomized to receive ezetimibe/simvastatin or atorvastatin.

MAIN OUTCOME MEASURE: The primary endpoint was the difference in the percent change of ApoB/ApoA1 at 12 weeks, and secondary endpoints were changes in lipid profiles, glycosylated hemoglobin (HbA1c), homeostatic model assessment (HOMA) index, and C-reactive protein.

RESULTS: In total, 132 patients (66 for each group) were enrolled and randomized. After 12 weeks of treatment, the ApoB/ApoA1 ratio was significantly reduced in both groups; however, the difference of changes between the two groups was not statistically significant (ezetimibe/simvastatin -38.6 + 18.0 % vs atorvastatin -34.4 + 15.5 %; p = 0.059). There were no significant differences in changes to total cholesterol, LDL cholesterol, high-density lipoprotein cholesterol, triglycerides, ApoB, and ApoB48 between the two groups. However, the increments of ApoA1 were significantly greater in the ezetimibe/simvastatin group than in the atorvastatin group (2.8 + 10.0 vs -1.8 + 9.8 %; p = 0.002). In the per-protocol analysis, improvement in ApoB/ApoA1 was significantly greater in the ezetimibe/simvastatin group (-42.8 + 11.8 vs -36.7 + 13.2 %; p = 0.019). The changes in HbA1c, HOMA index, and C-reactive protein were

comparable between the two groups. The adverse reaction rate was similar between the two groups (24.2 vs 34.9 %; p = 0.180).

CONCLUSION: Ezetimibe/simvastatin 10/20 mg is comparable to atorvastatin 20 mg for the management of dyslipidemia, and may have more favorable effects on apolipoprotein profiles than atorvastatin 20 mg in Korean patients with type 2 diabetes mellitus.

Liu, Z., et al. (2017). "Therapeutic effects of atorvastatin and ezetimibe compared with double-dose atorvastatin in very elderly patients with acute coronary syndrome." Oncotarget **8**(25): 41582-41589.

Objective Compared the effect of atorvastatin 10 mg combined ezetimibe 10 mg therapy with atorvastatin 20 mg on the long-term outcomes in very elderly patients with acute coronary syndrome. Methods A total of 230 octogenarian patients with acute coronary syndrome underwent coronary angiography were randomized to combined therapy group (atorvastatin 10 mg/d and ezetimibe 10 mg/d, n=114) or double-dose atorvastatin group (atorvastatin 20mg/d, n=116). The primary end point was one-year incidence of major adverse cardiovascular events (including cardiac death, spontaneous myocardial infarction, unplanned revascularization). Result At the end of one year, the percentage of patients with low-density lipoprotein cholesterol level decreased more than 30% or 50% were comparable between the two groups (93.5% vs. 90.1%, p= 0.36; 54.6% vs. 49.6%, p= 0.45). The rate of major adverse cardiovascular events in combined therapy group was similar with double-dose atorvastatin group (23.2% vs. 19.8%, p=0.55). In COX regression model, the risk of major adverse cardiovascular events in combined group isn't significantly higher than double-dose atorvastatin group (HR [95% CI] 1.12 [0.51 to 2.55], p = 0.74). The patients whose alanine aminotransferase increasing more than upper normal limit in combined group was lower than double-dose atorvastatin group (2.8% vs. 9.0%, p = 0.05). Conclusions For very elderly patients with acute coronary syndrome, atorvastatin combining ezetimibe induced similar long-term outcomes compared with double-dose atorvastatin but with less liver dysfunction. Copyright (C) Zhi Liu et al.

Masuda, J., et al. (2015). "Effect of combination therapy of ezetimibe and rosuvastatin on regression of coronary atherosclerosis in patients with coronary artery disease." International Heart Journal **56**(3): 278-285.

Ezetimibe has been reported to provide significant incremental reduction in low-density-lipoprotein cholesterol (LDL-C) when added to a statin; however, its effect on coronary atherosclerosis has not yet been evaluated in detail. The aim of this study was to investigate the add-on effect of ezetimibe to a statin on coronary atherosclerosis evaluated by intravascular ultrasound (IVUS).In this prospective randomized open-label study, a total of 51 patients with stable coronary artery disease (CAD) requiring percutaneous coronary intervention (PCI) were enrolled, and assigned to a combination group (n = 26, rosuvastatin 5 mg/day + ezetimibe 10 mg/day) or a monotherapy group (n = 25, rosuvastatin 5 mg/day). Volumetric IVUS analyses were performed at baseline and 6 months after the treatment for a non-PCI site. LDL-C level was significantly reduced in the combination group (-55.8%) versus that in the monotherapy group (-36.8%; P = 0.004). The percent change in plaque volume (PV), the primary endpoint, appeared to decrease more effectively in the combination group compared with the monotherapy group (-13.2% versus -3.1%, respectively, P = 0.050). Moreover, there was a significant

group x time interaction in the effects of the two treatments on PV (P = 0.021), indicating the regressive effect of the combination therapy on PV was greater than that of monotherapy for subtly different values of baseline PV in the two treatment groups. Moreover, percent change in PV showed positive correlations with percent change of LDL-C (r = 0.384, P = 0.015).Intensive lipid-lowering therapy with ezetimibe added to usual-dose statin may provide significant incremental reduction in coronary plaques compared with usual-dose statin monotherapy.

Matsushita, K., et al. (2016). "Effects of 4 Statins on Regression of Coronary Plaque in Acute Coronary Syndrome." Circulation Journal **80**(7): 1634-1643.

BACKGROUND: There is no information on differences in the effects of moderate- and low-intensity statins on coronary plaque in patients with acute coronary syndrome (ACS). The aim of this study was to compare the effects of 4 different statins in patients with ACS, using intravascular ultrasound (IVUS).

METHODS AND RESULTS: A total of 118 patients with ACS who underwent IVUS before percutaneous coronary intervention and who were found to have mild to moderate non-culprit coronary plaques were randomly assigned to receive either 20 mg/day atorvastatin or 4 mg/day pitavastatin (moderate-intensity statin therapy), or 10 mg/day pravastatin or 30 mg/day fluvastatin (low-intensity statin therapy). IVUS at baseline and at end of 10-month treatment was available in 102 patients. Mean percentage change in plaque volume (PV) was -11.1+/-12.8%, -8.1+/-16.9%, 0.4+/-16.0%, and 3.1+/-20.0% in the atorvastatin, pitavastatin, pravastatin, and fluvastatin groups, respectively (P=0.007, ANOVA). Moderate-intensity statin therapy induced regression of PV, whereas low-intensity statin therapy produced insignificant progression (-9.6% vs. 1.8%, P<0.001). On multivariate linear regression analysis, moderate-intensity statin therapy (P=0.02) and uric acid at baseline (P=0.02) were significant determinants of large percent PV reduction. LDL-C at follow-up did not correlate with percent PV change.

CONCLUSIONS: Moderate-intensity statin therapy induced regression of coronary PV, whereas low-intensity statin therapy resulted in slight progression of coronary PV in patients with ACS. (Circ J 2016; 80: 1634-1643).

Moreira, F. T., S. C. Ramos, et al. (2014). "Effects of two lipid lowering therapies on immune responses in hyperlipidemic subjects." Life Sciences **98**(2): 83-87.

AIMS: To compare the effects of two of the most effective lipid-lowering therapies with similar LDL-cholesterol reduction capacity on the innate and adaptive immune responses through the evaluation of autoantibodies anti-oxidized LDL (anti-oxLDL Abs) and electronegative LDL [LDL(-)] levels.

MAIN METHODS: We performed a prospective, randomized, open label study, with parallel arms and blinded endpoints. One hundred and twelve subjects completed the study protocol and received rosuvastatin 40 mg or ezetimibe/simvastatin 10/40 mg for 12 weeks. Lipids, apolipoproteins, LDL(-), and anti-oxLDL Abs (IgG) were assayed at baseline and end of study.

KEY FINDINGS: Main clinical and laboratory characteristics were comparable at baseline. Lipid modifications were similar in both treatment arms, however, a significant raise in anti-oxLDL Abs levels was observed in subjects treated with rosuvastatin (p=0.026 vs baseline), but not in those receiving simvastatin/ezetimibe. (p=0.233 vs baseline), thus

suggesting modulation of adaptive immunity by a potent statin. Titers of LDL(-) were not modified by the treatments.
SIGNIFICANCE: Considering atherosclerosis as an immune disease, this study adds new information, showing that under similar LDL-cholesterol reduction, the choice of lipid-lowering therapy can differently modulate adaptive immune responses. Copyright 2014 Elsevier Inc. All rights reserved.

Moutzouri, E., E. N. Liberopoulos, et al. (2013). "Effects of statin monotherapy versus statin plus ezetimibe combination on serum uric acid levels." Journal of Cardiovascular Pharmacology & Therapeutics 18(1): 13-18.

BACKGROUND: Uric acid is considered a risk factor for cardiovascular disease (CVD). The effect of statins and ezetimibe on serum uric acid levels has not been yet clarified.
OBJECTIVE: To compare the effect of simvastatin/ezetimibe 10/10 mg, simvastatin 40 mg, and rosuvastatin 10 mg daily on serum uric acid levels in patients with dyslipidemia.
METHODS: This was a prospective, randomized, open-label, blinded end point (PROBE) study. Following a 3-month dietary intervention, patients with hypercholesterolemia received simvastatin/ezetimibe 10/10 mg or simvastatin 40 mg or rosuvastatin 10 mg. Changes in serum levels of uric acid and fractional renal excretion of uric acid as well as changes in electrolyte and renal function parameters were assessed after 12 weeks of treatment.
RESULTS: One hundred fifty-three patients (56 male) were included. At week 12, a significant reduction in serum uric acid levels was seen in all treatment groups (simvastatin/ezetimibe 10/10 mg: -3.8%, simvastatin 40 mg: -5.7%, and rosuvastatin 10 mg: -3.8%; P < .05 compared with baseline; P = not significant [NS] for comparison between groups). Fractional excretion of uric acid nonsignificantly increased in all groups (simvastatin/ezetimibe 10/10 mg: +6.8%, simvastatin 40 mg: +6.8%, and rosuvastatin 10 mg: +5.9%). The reduction in serum uric acid levels correlated with the increase in fractional excretion of uric acid and baseline uric acid levels. Renal function parameters as well as serum levels and fractional excretions of electrolytes remained unchanged in all groups. Changes in serum lipids were similar across groups.
CONCLUSION: Simvastatin/ezetimibe 10/10 mg, simvastatin 40 mg, and rosuvastatin 10 mg exhibit a similar uric acid-lowering effect.

Murphy, S. A., C. P. Cannon, et al. (2009). "Reduction in recurrent cardiovascular events with intensive lipid-lowering statin therapy compared with moderate lipid-lowering statin therapy after acute coronary syndromes from the PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22) trial." Journal of the American College of Cardiology 54(25): 2358-62.

OBJECTIVES: In addition to reducing first events in patients after an acute coronary syndrome (ACS), we hypothesized that high-dose atorvastatin 80 mg would also reduce recurrent cardiovascular events, and therefore total events, compared with pravastatin 40 mg during the 2-year follow-up. BACKGROUND: In the PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22) trial, more intensive lipid lowering with high-dose atorvastatin reduced the first occurrence of the primary end point (death, myocardial infarction, unstable angina requiring rehospitalization, stroke, or revascularization > or = 30 days) compared with moderate lipid lowering with pravastatin. METHODS: Poisson regression

analysis was performed to compare the number of occurrences of the primary end point between high-dose atorvastatin and pravastatin in the PROVE IT-TIMI 22 trial. RESULTS: As previously reported, first primary end point events were reduced by 16% with atorvastatin 80 mg versus pravastatin 40 mg (n = 464 vs n = 537, respectively; p = 0.005). Additional events were also reduced by 19% with atorvastatin 80 mg (n = 275 vs n = 340, respectively; p = 0.009). Overall, there were 138 fewer primary efficacy events with atorvastatin 80 mg versus pravastatin 40 mg (n = 739 vs n = 877, respectively; rate ratio: 0.85, 95% confidence interval: 0.77 to 0.94, p = 0.001). CONCLUSIONS: Although analytic techniques commonly used in clinical outcomes trials censor patients who experience a component of the primary composite end point, total cardiovascular events are important to patients, clinicians, and health care payers. Maintaining low levels of low-density lipoprotein cholesterol is central to preventing additional atherosclerotic development and subsequent cardiovascular events. Atorvastatin 80 mg, a more intensive low-density lipoprotein cholesterol lowering agent, reduced both first and subsequent primary end point events compared with pravastatin 40 mg after ACS.

Murphy, S. A., et al. (2016). "Reduction in Total Cardiovascular Events With Ezetimibe/Simvastatin Post-Acute Coronary Syndrome: The IMPROVE-IT Trial." Journal of the American College of Cardiology **67**(4): 353-361.

BACKGROUND: Intensive low-density lipoprotein cholesterol therapy with ezetimibe/simvastatin in IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial) significantly reduced the first primary endpoint (PEP) in patients post-acute coronary syndrome (ACS) compared to placebo/simvastatin.

OBJECTIVES: This analysis tested the hypothesis that total events, including those beyond the first event, would also be reduced with ezetimibe/simvastatin therapy.

METHODS: All PEP events (cardiovascular [CV] death, myocardial infarction [MI], stroke, unstable angina [UA] leading to hospitalization, coronary revascularization >30 days post-randomization) during a median 6-year follow-up were analyzed in patients randomized to receive ezetimibe/simvastatin or placebo/simvastatin in IMPROVE-IT. Negative binomial regression was used for the primary analysis.

RESULTS: Among 18,144 patients, there were 9,545 total PEP events (56% were first events and 44% subsequent events). Total PEP events were significantly reduced by 9% with ezetimibe/simvastatin vs placebo/simvastatin (incidence-rate ratio [RR]: 0.91; 95% confidence interval [CI]: 0.85 to 0.97; p = 0.007), as were the 3 pre-specified secondary composite endpoints and the exploratory composite endpoint of CV death, MI, or stroke (RR: 0.88; 95% CI: 0.81 to 0.96; p = 0.002). The reduction in total events was driven by decreases in total nonfatal MI (RR: 0.87; 95% CI: 0.79 to 0.96; p = 0.004) and total NF stroke (RR: 0.77; 95% CI: 0.65 to 0.93; p = 0.005).

CONCLUSIONS: Lipid-lowering therapy with ezetimibe plus simvastatin improved clinical outcomes. Reductions in total PEP events, driven by reductions in MI and stroke, more than doubled the number of events prevented compared with examining only the first event. These data support continuation of intensive combination lipid-lowering therapy after an initial CV event. (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial [IMPROVE-IT]; NCT00202878).

Murrow, J. R., S. Sher, et al. (2012). "The differential effect of statins on oxidative stress and endothelial function: atorvastatin versus pravastatin." Journal of Clinical Lipidology 6(1): 42-49.

BACKGROUND: Atherogenic risk in subjects with metabolic syndrome is partly mediated by increased oxidative stress and subsequent endothelial dysfunction. Clinical trials have demonstrated differences in outcomes between subjects receiving lipophilic statins (atorvastatin) compared with hydrophilic statins (pravastatin). However, whether these findings are attributable to differences in the doses administered or to nonlipid-lowering pleiotropic effects of statins on oxidative stress and vascular function remains unknown. We hypothesized that equipotent doses of these two statins will have divergent effects on markers of oxidative stress and endothelial function.

METHODS: Thirty-six subjects with hyperlipidemia and metabolic syndrome and/or diabetes were randomized in a double-blind manner to either pravastatin 80 mg or atorvastatin 10 mg daily. Oxidative stress (dROMs assay that measures lipid hydroperoxides, plasma thiobarbituric acid reactive substances [TBARS], and aminothiol levels) and brachial artery flow-mediated dilation (FMD) were measured at baseline and after 12 weeks of statin therapy.

RESULTS: Statin therapy reduced serum low-density lipoprotein cholesterol levels equally in both groups. Atorvastatin therapy was associated with a significant reduction in TBARS (P= .006) and dROMs levels (P= .02), which was not observed in subjects treated with pravastatin. Endothelial function improved with statin therapy (P= .02), but there was no difference between the statin groups.

CONCLUSION: In hyperlipidemic subjects with metabolic syndrome, atorvastatin is associated with a greater reduction in lipid markers of oxidation compared with pravastatin. Whether these effects are responsible for the outcome differences in trials comparing these agents needs further investigation. Copyright 2012 National Lipid Association. All rights reserved.

Nicholls, S. J., C. M. Ballantyne, et al. (2011). "Effect of two intensive statin regimens on progression of coronary disease." New England Journal of Medicine 365(22): 2078-2087.

BACKGROUND: Statins reduce adverse cardiovascular outcomes and slow the progression of coronary atherosclerosis in proportion to their ability to reduce low-density lipoprotein (LDL) cholesterol. However, few studies have either assessed the ability of intensive statin treatments to achieve disease regression or compared alternative approaches to maximal statin administration.

METHODS: We performed serial intravascular ultrasonography in 1039 patients with coronary disease, at baseline and after 104 weeks of treatment with either atorvastatin, 80 mg daily, or rosuvastatin, 40 mg daily, to compare the effect of these two intensive statin regimens on the progression of coronary atherosclerosis, as well as to assess their safety and side-effect profiles.

RESULTS: After 104 weeks of therapy, the rosuvastatin group had lower levels of LDL cholesterol than the atorvastatin group (62.6 vs 70.2 mg per deciliter [1.62 vs 1.82 mmol per liter], P<0.001), and higher levels of high-density lipoprotein (HDL) cholesterol (50.4 vs 48.6 mg per deciliter [1.30 vs 1.26 mmol per liter], P=0.01). The primary efficacy end point, percent atheroma volume (PAV), decreased by 0.99% (95% confidence interval [CI], -1.19 to -0.63) with atorvastatin and by 1.22% (95% CI, -1.52 to -0.90) with

rosuvastatin (P=0.17). The effect on the secondary efficacy end point, normalized total atheroma volume (TAV), was more favorable with rosuvastatin than with atorvastatin: -6.39 mm(3) (95% CI, -7.52 to -5.12), as compared with -4.42 mm(3) (95% CI, -5.98 to -3.26) (P=0.01). Both agents induced regression in the majority of patients: 63.2% with atorvastatin and 68.5% with rosuvastatin for PAV (P=0.07) and 64.7% and 71.3%, respectively, for TAV (P=0.02). Both agents had acceptable side-effect profiles, with a low incidence of laboratory abnormalities and cardiovascular events.

CONCLUSIONS: Maximal doses of rosuvastatin and atorvastatin resulted in significant regression of coronary atherosclerosis. Despite the lower level of LDL cholesterol and the higher level of HDL cholesterol achieved with rosuvastatin, a similar degree of regression of PAV was observed in the two treatment groups. (Funded by AstraZeneca Pharmaceuticals; ClinicalTrials.gov number, NCT000620542.).

Nicholls, S. J., et al. (2017). "Comparative effects of cholesteryl ester transfer protein inhibition, statin or ezetimibe on lipid factors: the ACCENTUATE trial." Atherosclerosis **261**: 12-18.

Background and aims The optimal approaches to management of patients treated with moderate statin doses on lipid parameters are unknown. The ACCENTUATE study aimed to compare the effects of adding the cholesteryl ester transfer protein inhibitor (CETP) evacetrapib, ezetimibe or increasing statin dose in atorvastatin-treated high-vascular risk patients on lipid parameters. Methods 366 patients with atherosclerotic cardiovascular disease (ASCVD) and/or diabetes were treated with atorvastatin 40 mg/day for 28 days prior to randomization to atorvastatin 40 mg plus evacetrapib 130 mg, atorvastatin 80 mg, atorvastatin 40 mg plus ezetimibe 10 mg or atorvastatin 40 mg plus placebo, daily for 90 days at 64 centers in the United States. Lipid parameters, safety and tolerability were measured. Results Addition of evacetrapib significantly reduced LDL-C (-33%) compared with ezetimibe (-27%, p=0.045), increasing statin dose (-6%) and statin alone (0%, p<0.001). Evacetrapib also decreased apoB by 23% compared to 19% with ezetimibe (p=0.06) and 7% with increased statin dose (p<0.001), and reduced Lp(a) by 29% (p<0.001 vs. other groups). Evacetrapib increased HDL-C (+125%), apoA-I (+46%), apoC-III (+50%) and apoE (+28%) (p<0.001 vs. other groups). Non-ABCA1-mediated efflux increased by 53% (p<0.001 vs. other groups) with evacetrapib. ABCA1-mediated efflux also increased by 13% with evacetrapib (p<0.001 vs. ezetimibe, p=0.002 vs. increasing statin dose, and p=0.004 vs. statin alone). Addition of evacetrapib to atorvastatin produced an increase in hsCRP compared with ezetimibe (p=0.02). Conclusions While evacetrapib improved traditional atherogenic and putative protective lipid measures compared with ezetimibe and increasing statin dose in patients with ASCVD and/or diabetes, it also adversely affected novel atherogenic risk factors. These findings may contribute to the lack of clinical benefit observed in the ACCELERATE trial. Copyright (C) 2017 Elsevier B.V.

Nohara, R., H. Daida, et al. (2012). "Effect of intensive lipid-lowering therapy with rosuvastatin on progression of carotid intima-media thickness in Japanese patients: Justification for Atherosclerosis Regression Treatment (JART) study.[Erratum appears in Circ J. 2012;76(2):522 Note: Fujii, Katsuhito [corrected to Fujiu, Katsuhito]; Hiroi, Yukio [added]; Konishi, Hakuoh [added]; Matsuki, Michihiro [added]; Matsuoka, Takaaki [added]; Okauchi, Seizo [added]; Ozaki, Akihiko [added];Satoi, Satoshi [added]; Sawaki, Daigo [added]; Takahashi, Maiko

[corrected to Takahashi, Makio]]." Circulation Journal 76(1): 221-229.

BACKGROUND: A recent trial in Western countries has shown that rosuvastatin slows progression of carotid intima-media thickness (IMT) in patients with modest carotid IMT thickening and elevated levels of low-density lipoprotein cholesterol (LDL-C). We conducted a prospective, randomized, open-label, blinded-endpoint trial to determine whether rosuvastatin is more effective than pravastatin in slowing progression of carotid IMT in Japanese patients.

METHODS AND RESULTS: Adult patients with hypercholesterolemia who had a maximum IMT >=1.1mm were randomly assigned to receive rosuvastatin or pravastatin. The primary endpoint was the percent change in the mean-IMT, which was measured by a single observer who was blinded to the treatment assignments. The trial was stopped on April 2011 according to the recommendation by the data and safety monitoring committee. A total of 348 patients (173 rosuvastatin; 175 pravastatin) were enrolled and 314 (159 rosuvastatin; 155 pravastatin) were included in the primary analysis. Mean (SD) percentage changes in the mean-IMT at 12 months were 1.91% (10.9) in the rosuvastatin group and 5.8% (12.0) in the pravastatin group, with a difference of 3.89% (11.5) between the groups (P=0.004). At 12 months, 85 patients (59.4%) in the rosuvastatin group achieved a LDL-C/high-density lipoprotein cholesterol ratio <=1.5 compared with 24 patients (16.4%) in the pravastatin group (P<0.0001).

CONCLUSIONS: Rosuvastatin significantly slowed progression of carotid IMT at 12 months compared with pravastatin.

Nozue, T., et al. (2016). "Effects of Statin Therapy on Plasma Proprotein Convertase Subtilisin/kexin Type 9 and Sortilin Levels in Statin-Naive Patients with Coronary Artery Disease." Journal of Atherosclerosis & Thrombosis **23**(7): 848-856.

AIM: Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a key regulator of serum low-density lipoprotein (LDL) cholesterol levels, and sortilin is linked to lipoprotein metabolism. Although statin therapy increases PCSK9 levels, effects of this therapy on plasma sortilin levels have not been evaluated. The purpose of the present study was to examine the effects of statins on plasma PCSK9 and sortilin levels, and association of statin-induced increase in PCSK9 levels with sortilin.

METHODS: Serum lipid levels and plasma PCSK9 and sortilin levels were measured at baseline and 8 months after statin therapy in 90 statin-naive patients with coronary artery disease (CAD). Pitavastatin 4 mg/day was used to treat 44 patients and pravastatin 20 mg/day to treat the remaining 46 patients.

RESULTS: For both statin groups, significant increases in hetero-dimer PCSK9 levels (pitavastatin: 31%, p<0.0001; pravastatin: 34%, p=0.03) and decreases in sortilin levels (pitavastatin: -8%, p=0.02; pravastatin: -16%, p=0.002) were observed. Although a reduction in LDL cholesterol was greater in the pitavastatin group than in the pravastatin group, no significant differences were observed in percentage changes in hetero-dimer PCSK9 and sortilin levels. A significant positive correlation was observed between percentage changes in hetero-dimer PCSK9 levels and those in sortilin levels (pitavastatin: r=0.359, p=0.02; pravastatin: r=0.276, p=0.06).

CONCLUSIONS: Use of pitavastatin and pravastatin increased plasma PCSK9 and decreased sortilin levels. Statin-induced increases in PCSK9 were associated with changes in sortilin in statin-naive patients with CAD.

Ogawa, H., et al. (2014). "Differences between rosuvastatin and atorvastatin in lipid-lowering action and effect on glucose metabolism in Japanese hypercholesterolemic patients with concurrent diabetes. Lipid-lowering with highly potent statins in hyperlipidemia with type 2 diabetes patients (LISTEN) study." Circulation Journal **78**(10): 2512-2515.

BACKGROUND: Little is known about the differences between standard-dose statins effects on glucose level and lipids in Japanese patients with diabetes mellitus (DM).

METHODS AND RESULTS: The 1,049 patients were randomly assigned to either the rosuvastatin group or atorvastatin group. There were no significant differences between the 2 groups in the effect on non-high-density lipoprotein cholesterol (non-HDL-C) and HbA1c at 12 months. However, physicians tended to switch to more intensive therapy for DM in the atorvastatin group.

CONCLUSIONS: Rosuvastatin 5 mg and atorvastatin 10 mg have a similar lowering effect on non-HDL-C, but might be different in terms of adverse effect on glucose levels.

Olsson, A. G., C. Lindahl, et al. (2011). "LDL cholesterol goals and cardiovascular risk during statin treatment: the IDEAL study." European Journal of Cardiovascular Prevention & Rehabilitation 18(2): 262-269.

AIMS: We assessed the proportion of patients treated with either simvastatin 20 or 40 mg or atorvastatin 80 mg who achieved low-density lipoprotein cholesterol (LDL-C) goals of 2.5 or 2.0 mmol/l in the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) study. We explored how lipoprotein components related to cardiovascular disease (CVD) outcomes in these groups.

METHODS AND RESULTS: For subjects who reached on-treatment LDL-C goals, Cox regression models were used to assess the ability of lipoprotein components to predict CVD events. Treatment with simvastatin or atorvastatin resulted in 40 per cent and 80 per cent of patients, respectively, reaching the 2.5 mmol/l goal and 12 per cent and 52 per cent, respectively, reaching the 2.0 mmol/l goal, after 1 year (all $p<0.001$ between groups). Adjusting for baseline LDL-C levels, hazard ratio (HR) for those reaching 2.0-2.5 mmol/l LDL-C versus those reaching <2.0 mmol/l was 1.16 (95% confidence interval [CI], 1.02-1.33, $p=0.023$). An increase of the apolipoprotein B/A1 (apoB/A1) ratio by 1 standard deviation in participants who reached 2.0 mmol/l showed a HR for CVD of 1.14 (95% CI, 1.04-1.25, $p=0.004$).

CONCLUSION: More CVD patients treated with atorvastatin than simvastatin achieved either LDL-C goal and those reaching the 2.0 mmol/l goal exhibited significantly less CVD than those only reaching 2.5 mmol/l. In those reaching the 2.0 mmol/l goal, the apoB/A1 ratio still bears a relation to CVD outcome. The use of apoB/A1 ratio may provide additional predictive value to that of LDL-C.

Ose, L., D. Budinski, et al. (2009). "Comparison of pitavastatin with simvastatin in primary hypercholesterolaemia or combined dyslipidaemia.[Erratum appears in Curr Med Res Opin. 2010 May;26(5):1046 Note: Dosage error in article text]." Current Medical Research and Opinion **25**(11): 2755-64.

OBJECTIVES: The primary objective of this study was to demonstrate equivalence of pitavastatin compared with simvastatin in the reduction of low-density lipoprotein cholesterol (LDL-C) levels in patients with primary hypercholesterolaemia or combined

dyslipidaemia. Secondary objectives included achievement of National Cholesterol Education Program Adult Treatment Panel (NECP) and European Atherosclerosis Society (EAS) LDL-C goals, comparison of other lipid parameters, and assessment of safety and tolerability of the two statins. RESEARCH DESIGN AND METHODS: A prospective, randomised, active-controlled double-blind, double-dummy, 12-week therapy trial was conducted in 857 patients with either primary hypercholesterolaemia or combined dyslipidaemia. The trial was designed to demonstrate the equivalence (non-inferiority of presumed equipotent doses) of pitavastatin compared with simvastatin. Patients were randomised to one of four groups: pitavastatin 2 mg/day, pitavastatin 4 mg/day, simvastatin 20 mg/day or simvastatin 40 mg/day. The main study limitation was restriction of the study population to those eligible for administration of simvastatin. Trial registration: This clinical trial has been registered at www.clinicaltrials.gov NCT# NCT00309777. RESULTS: Pitavastatin 2 mg showed significantly better reductions of LDL-C (p = 0.014), non-high-density lipoprotein cholesterol (non-HDL-C) (p = 0.021) and total cholesterol (TC) (p = 0.041) compared with simvastatin 20 mg and led to more patients achieving the EAS LDL-C treatment target. Reduction of LDL-C in the pitavastatin 2 mg group was 39% compared with 35% in the simvastatin 20 mg group. Pitavastatin 4 mg showed similar effects on all lipid parameters to simvastatin 40 mg. The reductions in LDL-C were 44% and 43%, respectively. The safety profiles of pitavastatin and simvastatin were similar at the two dose levels. Pitavastatin was considered superior to simvastatin in terms of percent reduction of LDL-C in the lower dose group comparison and proved to be equivalent to simvastatin in percent reduction of LDL-C in the higher-dose group. CONCLUSION: As compared with simvastatin, an established first-line lipid-lowering agent, pitavastatin is an efficacious treatment choice in patients with primary hypercholesterolaemia or combined dyslipidaemia.

Pedersen, T. R., N. B. Cater, et al. (2010). "Comparison of atorvastatin 80 mg/day versus simvastatin 20 to 40 mg/day on frequency of cardiovascular events late (five years) after acute myocardial infarction (from the Incremental Decrease in End Points through Aggressive Lipid Lowering [IDEAL] trial)." American Journal of Cardiology 106(3): 354-9.

Previous studies have demonstrated that benefits of intensive statin therapy compared to standard statin therapy begin shortly after an acute event and are continued up to 2 years of follow-up. However, whether efficacy and safety of intensive statin therapy in patients with a recent cardiac event are maintained in longer-term follow-up has not been evaluated. We conducted a post hoc analysis of a subgroup of 999 patients who had a first acute myocardial infarction (MI) <2 months before randomization in a prospective, open-label, blinded end-point evaluation trial of 8,888 patients with a history of MI that compared intensive statin therapy (atorvastatin 80 mg) to standard statin therapy (simvastatin 20 to 40 mg) over approximately 5 years of follow-up. We analyzed the same composite end point used in the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT) trial (death, MI, hospitalization for unstable angina, revascularization, and stroke). Rates of the composite end point were 44.7% (n = 226) in the simvastatin group and 37.9% (n = 187) in the atorvastatin group (hazard ratio 0.82, 95% confidence interval 0.67 to 0.99, p = 0.04). Although statistical power was smaller than that of the PROVE IT trial, the relative risk decrease observed at 5 years is consistent with that in the 2-year follow-up in PROVE IT. The 2 treatment regimens were

well tolerated. In conclusion, our analysis provides support for the strategy of placing patients with recent MI on intensive statin therapy and maintaining the high dose over the long term, beyond 2 years. Copyright (c) 2010 Elsevier Inc. All rights reserved.

Pitt, B., J. Loscalzo, et al. (2012). "Comparison of lipid-modifying efficacy of rosuvastatin versus atorvastatin in patients with acute coronary syndrome (from the LUNAR study)." American Journal of Cardiology 109(9): 1239-1246.

Patients with acute coronary syndrome are recommended for early aggressive low-density lipoprotein (LDL) cholesterol-lowering therapy. The LUNAR study compared the efficacy of rosuvastatin with that of atorvastatin in decreasing LDL cholesterol in patients with acute coronary syndrome. Adult patients with coronary artery disease who were hospitalized for an acute coronary syndrome within 48 hours of first symptoms were randomized (n = 825) to an open-label, once-daily treatment with rosuvastatin 20 mg (RSV20), rosuvastatin 40 mg (RSV40), or atorvastatin 80 mg (ATV80) for 12 weeks. Patients were evaluated at weeks 2, 6, and 12. The primary end point was treatment efficacy in lowering LDL cholesterol averaged over 6 to 12 weeks. Changes in other lipoproteins, including high-density lipoprotein (HDL) cholesterol, and safety were evaluated. Analysis of covariance was used to compare least squares mean differences between each rosuvastatin treatment arm and the atorvastatin arm. The efficacy of RSV40 in lowering LDL cholesterol was significantly greater than that of ATV80 (46.8% vs 42.7% decrease, p = 0.02). LDL cholesterol lowering by RSV20 was similar to that by ATV80. Increases in HDL cholesterol were significantly greater with RSV40 (11.9%, p <0.001) and RSV20 (9.7%, p <0.01) than with ATV80 (5.6%). RSV40 was also significantly more effective than ATV80 in improving most other secondary efficacy variables, whereas the effects of RSV20 on these parameters were generally similar to those of ATV80. All 3 treatments were generally well tolerated over 12 weeks. In conclusion, results from the LUNAR study show that RSV40 more effectively decreased LDL cholesterol, increased HDL cholesterol, and improved other blood lipid parameters than ATV80 in patients with acute coronary syndrome. Copyright 2012 Elsevier Inc. All rights reserved.

Puri, R., S. E. Nissen, et al. (2013). "Factors underlying regression of coronary atheroma with potent statin therapy." European Heart Journal **34**(24): 1818-1825.

AIMS: Statins can inhibit the progression of coronary atherosclerosis. We aimed to characterize clinical factors that associate with differing measures of coronary atheroma volume following potent statin therapy.

METHODS AND RESULTS: SATURN employed serial intravascular ultrasound (IVUS) to monitor changes in measures of coronary atheroma burden [total atheroma volume (TAV) and per cent atheroma volume (PAV)] in 1039 patients with coronary artery disease, treated with rosuvastatin (40 mg) or atorvastatin (80 mg) daily for 24 months. Rosuvastatin-treated patients demonstrated greater reductions in low-density lipoprotein cholesterol (LDL-C, 47 vs 40%, P < 0.001) and greater increases in high-density lipoprotein cholesterol (HDL-C, 13 vs 10%, P = 0.02). These alterations in the lipid profile associated with greater TAV (-6.4 vs -4.4 mm(3), P = 0.01), but not PAV (-1.22 vs -0.99%, P = 0.17) regression. Greater TAV reductions with rosuvastatin vs atorvastatin occurred in patients with diabetes (P = 0.01, treatment by diabetic status

interaction P-value 0.05). Greater PAV reductions with rosuvastatin were evident in females (P = 0.01, treatment by sex interaction P-value 0.03) and in those with greater than or equal to median baseline LDL-C (P = 0.02, treatment by LDL-C group interaction P-value 0.03) or HDL-C levels (P = 0.02, treatment by HDL-C group interaction P-value 0.04). On multivariable analysis assessing change in TAV and PAV, both higher baseline TAV and PAV independently associated with TAV and PAV regression, respectively (standardized estimates: TAV -0.25, P < 0.001; PAV -0.23, P < 0.001).

CONCLUSION: Higher-risk patients, particularly those with greater baseline coronary atheroma volume, are more likely to experience less disease progression with potent statin therapy.

Pytel, E., et al. (2017). "Effect of intensive lipid-lowering therapies on cholinesterase activity in patients with coronary artery disease." Pharmacological reports : PR **69**(1): 150-155.

METHODS: Plasma and erythrocytes were isolated from the peripheral blood of CAD patients (n=61) and healthy subjects (n=63). The patients were randomized into three groups: 20mg/day rosuvastatin, 40mg/day atorvastatin, and combined 10mg/day atorvastatin with 10mg/day ezetimibe. The following parameters were studied: activity of acetylcholinesterase (AChE) and butyrylcholinoesterase (BChE) and lipid levels. RESULTS: Patients with CAD demonstrated significant increase in AChE and BChE activity. We observed increase in the level of low-density lipoprotein cholesterol (LDL) and triglycerides (TG) level, and decrease in high density lipoprotein cholesterol (HDL) level. After atorvastatin monotherapy, the following decrease in activity were observed: 17% LDL, 43% total cholesterol (TC) level, 33% AChE and 17% BChE. The following decrease in activity were observed following rosuvastatin monotherapy: 26% LDL level, 26% AChE and 18% BChE. After combined atorvastatin+ezetimibe therapy, the following decrease in activity occurred: 27% of LDL level, 15% TC, 33% of AChE and 20% BChE. CONCLUSIONS: Our results suggest that intensive lipid-lowering therapy has a beneficial effect on AChE and BChE activity and lipid levels. Combination atorvastatin+ezetimibe therapy was found to have similar effects on the tested parameters as statin monotherapy. BACKGROUND: Many disease entities, including coronary artery disease (CAD), demonstrate abnormalities in the activity of cholinesterases. As CAD is characterized by an increase in cholesterol level, patients with this disease are treated with lipid-lowering drugs. The present study attempts to determine how statin or combined statin and ezetimibe therapy influences cholinesterase activity.

Ramos, S. C., F. A. Fonseca, et al. (2011). "The role of soluble fiber intake in patients under highly effective lipid-lowering therapy." Nutrition Journal 10: 80.

BACKGROUND: It has been demonstrated that statins can increase intestinal sterol absorption. Augments in phytosterolemia seems related to cardiovascular disease.

OBJECTIVE: We examined the role of soluble fiber intake in endogenous cholesterol synthesis and in sterol absorption among subjects under highly effective lipid-lowering therapy.

DESIGN: In an open label, randomized, parallel-design study with blinded endpoints, subjects with primary hypercholesterolemia (n = 116) were assigned to receive during 12 weeks, a daily dose of 25 g of fiber (corresponding to 6 g of soluble fibers) plus rosuvastatin 40 mg (n = 28), rosuvastatin 40 mg alone (n = 30), sinvastatin 40 mg plus ezetimibe 10 mg plus 25 g of fiber (n = 28), or sinvastatin 40 mg plus ezetimibe 10 mg (n = 30) alone.

RESULTS: The four assigned therapies produced similar changes in total cholesterol, LDL-

cholesterol, and triglycerides ($p < 0.001$ vs baseline) and did not change HDL-cholesterol. Fiber intake decreased plasma campesterol ($p < 0.001$ vs baseline), particularly among those patients receiving ezetimibe ($p < 0.05$ vs other groups), and -sitosterol ($p = 0.03$ vs baseline), with a trend for lower levels in the group receiving fiber plus ezetimibe ($p = 0.07$). Treatment with rosuvastatin alone or combined with soluble fiber was associated with decreased levels of desmosterol ($p = 0.003$ vs other groups). Compared to non-fiber supplemented individuals, those treated with fibers had weight loss ($p = 0.04$), reduced body mass index ($p = 0.002$) and blood glucose ($p = 0.047$).

CONCLUSION: Among subjects treated with highly effective lipid-lowering therapy, the intake of 25 g of fibers added favorable effects, mainly by reducing phytosterolemia. Additional benefits include improvement in blood glucose and anthropometric parameters.

Rosen, J. B., J. G. Jimenez, et al. (2013). "A comparison of efficacy and safety of an ezetimibe/simvastatin combination compared with other intensified lipid-lowering treatment strategies in diabetic patients with symptomatic cardiovascular disease." Diabetes & Vascular Disease Research **10**(3): 277-286.

The low-density lipoprotein cholesterol (LDL-C) lowering efficacy of switching to ezetimibe/simvastatin (EZ/S) 10/20 mg versus doubling the run-in statin dose (to simvastatin 40 mg or atorvastatin 20 mg) or switching to rosuvastatin 10 mg in subjects with cardiovascular disease (CVD) and diabetes was assessed. Endpoints included percentage change in LDL-C and percentage of patients achieving LDL-C <70 mg/dL. Significantly greater reductions in LDL-C occurred when switching to EZ/S versus statin doubling in the overall population and in subjects treated with simvastatin 20 mg or atorvastatin 10 mg (all $p < 0.001$). The LDL-C reduction was numerically greater when switching to EZ/S versus switching to rosuvastatin ($p = 0.060$). Significantly more subjects reached LDL-C <70 mg/dL with EZ/S (54.5%) versus statin doubling (27.0%) or rosuvastatin (42.5%) in the overall population (all $p < 0.001$) and within each stratum (all $p < 0.001$). Switching to EZ/S provided significantly greater reductions in LDL-C versus statin doubling and significantly greater achievement of LDL-C targets versus statin doubling or switching to rosuvastatin.

Rosen, J. B., et al. (2013). "Consistency of effect of ezetimibe/simvastatin compared with intensified lipid-lowering treatment strategies in obese and non-obese diabetic subjects." Lipids in Health & Disease **12**: 103.

PURPOSE: This post hoc analysis assessed switching to ezetimibe/simvastatin 10/20 mg vs doubling the baseline statin dose to simvastatin 40 mg or atorvastatin 20 mg or switching to rosuvastatin 10 mg in subgroups of obese (BMI>30 kg/m2) and non-obese (BMI<30 kg/m2) diabetic subjects.

METHODS: This was a randomized, double-blind, 12-week study of adults 18-79 years with cardiovascular disease with low-density lipoprotein cholesterol (LDL-C) >70 and <160 mg/dl. Percent change in LDL-C and other lipids was estimated.

RESULTS: In obese subjects (n=466), percent changes in LDL-C and most other lipids were greater with ezetimibe/simvastatin vs doubling the baseline statin dose or switching to rosuvastatin. In non-obese subjects (n=342), percent changes in LDL-C, total cholesterol, non-HDL-C, Apo B and Apo A-I were greater with ezetimibe/simvastatin vs doubling the baseline statin dose or switching to rosuvastatin; and treatment with

ezetimibe/simvastatin resulted in greater changes in triglycerides vs rosuvastatin and HDL-C vs doubling the baseline statin dose. The safety profiles were generally similar.
CONCLUSIONS: Regardless of baseline obesity status, switching to ezetimibe/simvastatin was more effective at reducing LDL-C, total cholesterol, non-HDL-C, and Apo B vs doubling the baseline statin dose to simvastatin 40 mg or atorvastatin 20 mg or switching to rosuvastatin 10 mg.

Saku, K., B. Zhang, et al. (2011). "Randomized head-to-head comparison of pitavastatin, atorvastatin, and rosuvastatin for safety and efficacy (quantity and quality of LDL): the PATROL trial." Circulation Journal 75(6): 1493-1505.

BACKGROUND: Atorvastatin, rosuvastatin and pitavastatin are available for intensive, aggressive low-density lipoprotein cholesterol (LDL-C)-lowering therapy in clinical practice. The objective of the Randomized Head-to-Head Comparison of Pitavastatin, Atorvastatin, and Rosuvastatin for Safety and Efficacy (Quantity and Quality of LDL) (PATROL) Trial was to compare the safety and efficacy of atorvastatin, rosuvastatin and pitavastatin head to head in patients with hypercholesterolemia. This is the first prospective randomized multi-center trial to compare these strong statins (UMIN Registration No: 000000586).
METHODS AND RESULTS: Patients with risk factors for coronary artery disease and elevated LDL-C levels were randomized to receive atorvastatin (10mg/day), rosuvastatin (2.5mg/day), or pitavastatin (2mg/day) for 16 weeks. Safety was assessed in terms of adverse event rates, including abnormal clinical laboratory variables related to liver and kidney function and skeletal muscle. Efficacy was assessed by the changes in the levels and patterns of lipoproteins. Three hundred and two patients (from 51 centers) were enrolled, and these 3 strong statins equally reduced LDL-C and LDL particles, as well as fast-migrating LDL (modified LDL) by 40-45%. Newly developed pitavastatin was non-inferior to the other 2 statins in lowering LDL-C. There were no differences in the rate of adverse drug reactions among the 3 groups, but HbA(1c) was increased while uric acid was decreased in the atorvastatin and rosuvastatin groups.
CONCLUSIONS: The safety and efficacy of these 3 strong statins are equal. It is suggested that the use of these 3 statins be completely dependent on physician discretion based on patient background.

Sardella, G., L. Lucisano, et al. (2013). "Comparison of high reloading ROsuvastatin and Atorvastatin pretreatment in patients undergoing elective PCI to reduce the incidence of MyocArdial periprocedural necrosis. The ROMA II trial." International Journal of Cardiology **168**(4): 3715-3720.

OBJECTIVES: The objective of this study is to compare a reloading dose of Rosuvastatin and Atorvastatin administered within 24 h before coronary angioplasty (PCI) in reducing the rate of periprocedural myonecrosis and major cardiac and cerebrovascular events (MACCE) in patients on chronic statin treatment undergoing elective PCI.
BACKGROUND: Elective PCI may be complicated with elevation of cardiac biomarkers. Several studies suggested that pretreatment with statins may be associated with a reduction in periprocedural myocardial necrosis.

METHODS: Three hundred and fifty patients with stable angina who underwent elective PCI were randomly assigned to receive a pre-procedural reloading dose of Rosuvastatin (40 mg) (Rosuvastatin Group-RG n=175) or Atorvastatin (80 mg) (Atorvastatin Group-AG n=175) and a control group on chronic statin therapy without reloading (Control-Group-CG). The primary end-point was periprocedural myocardial necrosis and the occurrence of MACCE at 30-day,6-12 month follow-up. Also we evaluate the rise of periprocedural Troponin T serum levels >3x the upper limit of normal.

RESULTS: Twelve and 24-hour post-PCI Creatine Kinase Muscle and Brain (CK-MB) elevation >3x occurred more frequently in the CG than in the RG and in the AG (at 24-h: 25.0 vs 7.1; p=0.003 and 25.0 vs 6.1; p=0.001). At 30-day, 6-and 12-month follow-up the incidence of cumulative MACCE was higher in CG than in the RG or AG (at 12-month: 41.0% vs 11.4% vs 12.0%; p=0.001). There was no difference between the RG and AG in terms of myocardial post-procedural necrosis and MACCE occurrence at follow-up.

CONCLUSIONS: High-dose statin reloading improves procedural and long term clinical outcomes in stable patients on chronic statin therapy. Both Rosuvastatin and Atorvastatin showed similar beneficial effects on procedural and long-term outcomes. 2013.

Sarma, A., et al. (2014). "The incidence of kidney injury for patients treated with a high-potency versus moderate-potency statin regimen after an acute coronary syndrome." Journal of the American Heart Association **3**(3): e000784.

BACKGROUND: Observational studies have raised concerns that high-potency statins increase the risk of acute kidney injury. We therefore examined the incidence of kidney injury across 2 randomized trials of statin therapy.

METHODS AND RESULTS: PROVE IT-TIMI 22 enrolled 4162 subjects after an acute coronary syndrome (ACS) and randomized them to atorvastatin 80 mg/day versus pravastatin 40 mg/day. A-to-Z enrolled 4497 subjects after ACS and randomized them to a high-potency (simvastatin 40 mg/day x 1 months, then simvastatin 80 mg/day) versus a delayed moderate-potency statin strategy (placebo x 4 months, then simvastatin 20 mg/day). Serum creatinine was assessed centrally at serial time points. Adverse events (AEs) relating to kidney injury were identified through database review. Across both trials, mean serum creatinine was similar between treatment arms at baseline and throughout follow-up. In A-to-Z, the incidence of a 1.5-fold or > 0.3 mg/dL rise in serum creatinine was 11.4% for subjects randomized to a high-potency statin regimen versus 12.4% for those on a delayed moderate-potency regimen (odds ratio [OR], 0.91; 95% confidence interval [CI], 0.76 to 1.10; P=0.33). In PROVE IT-TIMI 22, the incidence was 9.4% for subjects randomized to atorvastatin 80 mg/day and 10.6% for subjects randomized to pravastatin 40 mg/day (OR, 0.88; 95% CI, 0.71 to 1.09; P=0.25). Consistent results were observed for different kidney injury thresholds and in individuals with diabetes mellitus or with moderate renal dysfunction. The incidence of kidney injury-related adverse events (AEs) was not statistically different for patients on a high-potency versus moderate-potency statin regimen (OR, 1.06; 95% CI, 0.68 to 1.67; P=0.78).

CONCLUSIONS: For patients enrolled in 2 large randomized trials of statin therapy after ACS, the use of a high-potency statin regimen did not increase the risk of kidney injury.

Sasaki, J., T. Otonari, et al. (2013). "Effects of pravastatin and atorvastatin on HDL cholesterol and glucose metabolism in patients with dyslipidemia and glucose intolerance: the PRAT study." Journal of Atherosclerosis & Thrombosis **20**(4): 368-379.

AIMS: While statins have the property of increasing high-density lipoprotein cholesterol (HDL-C) in addition to lowering low-density lipoprotein cholesterol (LDL-C), a potential adverse effect on glucose metabolism has raised a concern over statin therapy. In a comparative trial, we investigated the effects of low-dose pravastatin and atorvastatin on HDL-C and glucose metabolism in patients with elevated LDL-C levels and glucose intolerance.

METHODS: Eligible patients were men aged >20 years or postmenopausal women who had LDL-C >140 mg/dL, HDL-C <80 mg/dL, and triglycerides <500 mg/dL and who had glucose intolerance. The patients were randomly allocated to either pravastatin (10 mg/day) or atorvastatin (10 mg/day) treatment for 12 months in an unblinded fashion. The percent changes from the baseline were compared between the treatments.

RESULTS: Of 202 patients who were randomized to either of the two treatments, 195 patients started the study medication, and 187 patients underwent the follow-up measurements at 6 or 12 months (pravastatin, n= 93; atorvastatin, n= 94). HDL-C increased by 4.3% (p= 0.03) in the pravastatin group and by 5.8% (p=0.0005) in the atorvastatin group and showed no between-group difference (p= 0.38). LDL-C decreased substantially in both groups (pravastatin, 21.5%; atorvastatin, 35.5%), and the decrease was much greater in the atorvastain group (p<0.0001). HbA1c slightly increased in both groups, but showed no measurable difference in the increase between the two treatments (p=0.30).

CONCLUSION: Pravastatin and atorvastatin of 10 mg per day each increased HDL-C by almost the same extent. These two statins did not show a differential effect on glucose metabolism.

Scheffer, P. G., R. K. Schindhelm, et al. (2013). "No effect of atorvastatin and simvastatin on oxidative stress in patients at high risk for cardiovascular disease." Netherlands Journal of Medicine **71**(7): 359-365.

BACKGROUND: Statins are thought to have anti-atherogenic effects beyond cholesterol lowering. One such mechanism may involve reduction of oxidative stress. The aim of our study was to investigate and to compare the oxidative stress lowering capacity of atorvastatin with that of simvastatin in patients at high risk for cardiovascular disease using conventional markers and sensitive markers measured by highly specific techniques such as liquid chromatography tandem mass spectrometry.

METHODS: We included 30 statin-naive patients with diabetes mellitus, and/or obesity, and/or hypertension (12 male, 18 female, mean age 44.8+11.1 years), and randomised them to receive either atorvastatin 10 mg or simvastatin 40 mg daily to obtain an equimolar cholesterol reduction. Blood and urine samples were obtained at baseline and at 1, 6 and 12 weeks.

RESULTS: Low-density lipoprotein (LDL) cholesterol and coenzyme Q10 decreased significantly in both groups. Simvastatin caused a faster initial LDL cholesterol lowering than atorvastatin (p=0.01), but the overall effect after 12 weeks of atorvastatin and simvastatin was similar. Plasma myeloperoxidase and malondialdehyde did not change during the study period in the two groups. Urinary F2-isoprostanes decreased gradually and significantly in the atorvastatin group but not in the simvastatin group, but the

between-group difference was not significant. Urinary 8-hydroxy-2-deoxyguanosine did not change in the two groups.

Shimabukuro, M., M. Higa, et al. (2011). "Distinct effects of pitavastatin and atorvastatin on lipoprotein subclasses in patients with Type 2 diabetes mellitus." Diabetic Medicine 28(7): 856-864.

AIMS: Effects of pitavastatin and atorvastatin on the lipid profile and lipoprotein subclasses were compared in patients with Type 2 diabetes with dyslipidaemia.

METHODS: Patients with Type 2 diabetes with hypercholesterolaemia and/or hypertriglyceridaemia were randomized to receive pitavastatin 2 mg (n = 16) or atorvastatin 10 mg (n = 15) for 6 months, and blood lipid and lipoprotein profiles and cholesterol and triglyceride contents of 20 lipoprotein subclasses, determined by high-performance liquid chromatography, were compared.

RESULTS: At baseline, cholesterol in VLDL and LDL subclasses were increased equally in two groups of patients with diabetes as compared with normolipidaemic control subjects. As compared with baseline, serum levels of total cholesterol, LDL cholesterol, non-HDL cholesterol, LDL cholesterol:HDL cholesterol ratio and apolipoprotein B were decreased after 1, 3 and 6 months of treatment with atorvastatin and pitavastatin. Serum triglyceride levels were decreased after 1, 3 and 6 months of atorvastatin, but only at 3 months of pitavastatin. Serum HDL cholesterol was increased after 1, 3 and 6 months of pitavastatin, whereas HDL cholesterol was even decreased after 6 months of atorvastatin. Cholesterol levels of most VLDL and LDL subclasses were decreased equally in both groups. However, only pitavastatin increased cholesterol of medium HDL subclass. Serum triglyceride and triglyceride contents in VLDL and LDL subclasses were decreased only by atorvastatin.

CONCLUSIONS: The impact on lipoprotein subclass profiles was different between pitavastatin and atorvastatin. It may be beneficial to determine lipoprotein subclass profile and select the appropriate statin for each profile in patients with diabetes with an additional cardiovascular risk such as low HDL cholesterol or hypertriglyceridaemia. 2011 The Authors. Diabetic Medicine 2011 Diabetes UK.

Shioji, K., et al. (2014). "Achievement rates of Japan Atherosclerosis Society Guidelines 2007 LDL-cholesterol goals with rosuvastatin or atorvastatin in patients who had not achieved their goal with atorvastatin." Cardiovascular therapeutics **32**(3): 97-104.

BACKGROUND: The Japan Atherosclerosis Society's 2007 Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases (JAS2007GL) advocate reducing LDL cholesterol (LDL-C) to target levels in patients with dyslipidemia, but achievement rates are frequently unsatisfactory even in the presence of lipid-lowering therapy. This multicenter, open-label, randomized, parallel-group study compared the efficacy of rosuvastatin and atorvastatin on JAS2007GL LDL-C goals in Japanese patients not achieving their target goal with atorvastatin treatment.

METHODS: The study involved 20 clinical institutes in Japan (Kishiwada Atherosclerosis Prevention Study [KAPS] Group). Patients with category II or III risk of coronary artery disease (CAD), or those with a history of CAD (secondary prevention), who had not achieved their JAS2007GL LDL-C goals during treatment with atorvastatin for at least 4 weeks were switched either to rosuvastatin 5 mg/day (from atorvastatin 10 mg/day) or

rosuvastatin 10 mg/day (from atorvastatin 20 mg/day) (n = 75) or continued to receive atorvastatin (n = 77). The primary endpoint was achievement of LDL-C goals at 3 months. The main secondary endpoint was achievement of LDL-C goal + high-sensitivity C-reactive protein level <1.0 mg/L at 3 months.

RESULTS: Achievement rates for the primary endpoint were 49.3% in the rosuvastatin group and 31.7% in the atorvastatin group (P = 0.022). Achievement rates for the main secondary endpoint were 40.0% in the rosuvastatin group and 20.8% in the atorvastatin group (P = 0.010). Rosuvastatin and atorvastatin were both well tolerated in this study.

CONCLUSIONS: Rosuvastatin is a useful treatment option for Japanese patients who are not achieving their JAS2007GL LDL-C goal with atorvastatin.

Sponseller, C. A., et al. (2014). "Comparison of the lipid-lowering effects of pitavastatin 4 mg versus pravastatin 40 mg in adults with primary hyperlipidemia or mixed (combined) dyslipidemia: a Phase IV, prospective, US, multicenter, randomized, double-blind, superiority trial." Clinical Therapeutics **36**(8): 1211-1222.

PURPOSE: Results from a Phase III, European, non-inferiority trial in elderly (age >65 years) patients with primary hyperlipidemia or mixed (combined) dyslipidemia demonstrated significantly greater reductions in LDL-C for pitavastatin versus pravastatin across 3 pair-wise dose comparisons (1 mg vs 10 mg, 2 mg vs 20 mg, and 4 mg vs 40 mg, respectively). The present study investigated whether pitavastatin 4 mg is superior to pravastatin 40 mg in LDL-C reduction in adults (18-80 years old) with primary hyperlipidemia or mixed (combined) dyslipidemia.

METHODS: This was a Phase IV, multicenter, randomized, double-blind, double-dummy, active-control superiority study conducted in the United States. Patients with baseline LDL-C levels of 130 to 220 mg/dL (inclusive) and triglyceride levels <400 mg/dL after a 6-week washout/dietary stabilization period were randomized to 12 weeks of once-daily treatment with either pitavastatin 4 mg or pravastatin 40 mg.

FINDINGS: A total of 328 subjects (164 per treatment arm) were randomized (mean age, 57.9 years [76% were aged <65 years]; 49.4% women; mean body mass index, 30.2 kg/m(2)) to treatment. The median percent change in LDL-C from baseline to the week 12 endpoint was -38.1% for pitavastatin 4 mg and -26.4% for pravastatin 40 mg; the difference in median percent change between treatments was -12.5% (P < 0.001). Differences between treatments in median percent reductions from baseline for apolipoprotein B, total cholesterol, and non-HDL-C were also significant in favor of pitavastatin (P < 0.001). Both treatments significantly (P < 0.001) increased HDL-C and decreased triglycerides, but the differences between treatments were not statistically significant. The overall rate of treatment-emergent adverse events was 47.6% (78 of 164) for pitavastatin and 44.5% (73 of 164) for pravastatin. Myalgia was reported by 3 patients (1.8%) in the pitavastatin group and by 4 patients (2.4%) in the pravastatin group. There were no reports of myositis or rhabdomyolysis.

IMPLICATIONS: Pitavastatin 4 mg demonstrated superior LDL-C reductions compared with pravastatin 40 mg after 12 weeks of therapy in adults with primary hyperlipidemia or mixed (combined) dyslipidemia. There were no new safety findings in the trial. Clinical Trials.gov identifier: NCT01256476.

Stegman, B., et al. (2014). "High-intensity statin therapy alters the natural history of diabetic coronary atherosclerosis: insights from SATURN." Diabetes Care **37**(11): 3114-3120.

OBJECTIVE: Although statins can induce coronary atheroma regression, this benefit has yet to be demonstrated in diabetic individuals. We tested the hypothesis that high-intensity statin therapy may promote coronary atheroma regression in patients with diabetes.

RESEARCH DESIGN AND METHODS: The Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin (SATURN) used serial intravascular ultrasound measures of coronary atheroma volume in patients treated with rosuvastatin 40 mg or atorvastatin 80 mg for 24 months. This analysis compared changes in biochemistry and coronary percent atheroma volume (PAV) in patients with (n = 159) and without (n = 880) diabetes.

RESULTS: At baseline, patients with diabetes had lower LDL cholesterol (LDL-C) and HDL cholesterol (HDL-C) levels but higher triglyceride and CRP levels compared with patients without diabetes. At follow-up, diabetic patients had lower levels of LDL-C (61.0 +/- 20.5 vs. 66.4 +/- 22.9 mg/dL, P = 0.01) and HDL-C (46.3 +/- 10.6 vs. 49.9 +/- 12.0 mg/dL, P < 0.001) but higher levels of triglycerides (127.6 [98.8, 163.0] vs. 113.0 mg/dL [87.6, 151.9], P = 0.001) and CRP (1.4 [0.7, 3.3] vs. 1.0 [0.5, 2.1] mg/L, P = 0.001). Both patients with and without diabetes demonstrated regression of coronary atheroma as measured by change in PAV (-0.83 +/- 0.13 vs. -1.15 +/- 0.13%, P = 0.08). PAV regression was less in diabetic compared with nondiabetic patients when on-treatment LDL-C levels were >70 mg/dL (-0.31 +/- 0.23 vs. -1.01 +/- 0.21%, P = 0.03) but similar when LDL-C levels were <70 mg/dL (-1.09 +/- 0.16 vs. -1.24 +/- 0.16%, P = 0.50).

CONCLUSIONS: High-intensity statin therapy alters the progressive nature of diabetic coronary atherosclerosis, yielding regression of disease in diabetic and nondiabetic patients.Copyright © 2014 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered.

Stender, S., D. Budinski, et al. (2013). "Pitavastatin shows greater lipid-lowering efficacy over 12 weeks than pravastatin in elderly patients with primary hypercholesterolaemia or combined (mixed) dyslipidaemia." European Journal of Preventive Cardiology 20(1): 40-53.

AIM: To compare the safety and efficacy of once-daily pitavastatin (1, 2, and 4 mg) and pravastatin (10, 20, and 40 mg) in elderly patients (>= 65 years of age) with primary hypercholesterolaemia or combined (mixed) dyslipidaemia.

DESIGN: After a 6-8-week washout/dietary period, patients were randomized to six treatment groups (1, 2, or 4 mg pitavastatin vs 10, 20, or 40 mg pravastatin) in a 12-week multicentre double-blind study. Patients (n = 942; men, 44.3%; Caucasian, 99.3%; mean age, 70 years; age range, 65-89 years) in all groups were well matched for duration of disease and diagnosis.

RESULTS: Mean decreases in low-density lipoprotein cholesterol over 12 weeks were 31.4-44.3% with pitavastatin 1-4 mg and 22.4-34.0% with pravastatin 10-40 mg (p < 0.001 for all dose comparisons). Compared with pravastatin, pitavastatin provided greater decreases in total cholesterol and apolipoprotein B in all dose groups (p < 0.001) and triglycerides in the low-dose (p = 0.001) and higher-dose (p = 0.016) groups, and greater

increases in high-density lipoprotein cholesterol in the intermediate-dose (p = 0.013) and higher-dose (p = 0.023) groups. The proportions of patients achieving the European Atherosclerosis Society target with pitavastatin and pravastatin, respectively, were: low doses, 59.9 and 37.9%; intermediate doses, 79.5 and 51.0%; higher doses, 88.1 and 65.7% (p < 0.001 for all comparisons). Both statins were well tolerated, with no reports of myopathy or rhabdomyolysis.
CONCLUSION: Pitavastatin provides superior efficacy and comparable tolerability to pravastatin in elderly patients.

Stoekenbroek, R. M., et al. (2015). "High-dose atorvastatin is superior to moderate-dose simvastatin in preventing peripheral arterial disease." Heart **101**(5): 356-362.
OBJECTIVES: To study whether high-dose versus usual-dose statin treatment reduces the incidence of peripheral artery disease (PAD) and what is the effect of high-dose statin treatment on cardiovascular disease (CVD) outcome in patients with PAD.
METHODS AND RESULTS: In the Incremental Decrease in End Points Through Aggressive Lipid Lowering trial, 8888 post-myocardial infarction patients were randomised to high-dose or usual-dose statin therapy (atorvastatin 80 mg/day vs simvastatin 20-40 mg/day). We investigated the effect of high-dose versus usual-dose statins on the pre-specified outcome PAD incidence, and additionally performed a posthoc analysis of the efficacy of high-dose statins in reducing CVD risk among patients with PAD. During a median follow-up of 4.8 years, 94 patients (2.2%) receiving atorvastatin and 135 patients (3.2%) receiving simvastatin developed PAD (HR=0.70, 95% CI 0.53 to 0.91; p=0.007). The risk of major coronary events was almost twofold higher in patients with PAD at baseline, but was no longer significant after adjusting for the adverse cardiovascular risk profile. In PAD patients, major coronary events occurred in fewer patients in the atorvastatin group (14.4%) than in the simvastatin group (20.1%), but the difference did not reach statistical significance. (HR=0.68, 95% CI 0.41 to 1.11; p=0.13). Atorvastatin treatment significantly reduced overall cardiovascular (p=0.046) and coronary events (p=0.004), and coronary revascularisation (p=0.007) in these patients.
CONCLUSIONS: High-dose statin therapy with atorvastatin significantly reduced the incidence of PAD compared with usual-dose statin therapy with simvastatin. Patients with a history of PAD at baseline were at higher risk of future coronary events and this risk was reduced by high-dose atorvastatin treatment.
TRIAL REGISTRATION NUMBER: NCT00159835 (URL: http://clinicaltrials.gov/show/NCT00159835).Copyright Published by the BMJ Publishing Group Limited. For permission to use (where not already granted under a licence) please go to http://group.bmj.com/group/rights-licensing/permissions.

Tani, S., et al. (2015). "Contribution of apolipoprotein A-I to the reduction in high-sensitivity C-reactive protein levels by different statins: comparative study of pitavastatin and atorvastatin." Heart & Vessels **30**(6): 762-770.
Recently, investigation may have focused on modification of apolipoprotein A-I (apoA-I) associated with anti-inflammatory effect for the potential prevention of cardiovascular events. The purpose of this study was to evaluate the effects of atorvastatin and pitavastatin on serum apoA-I levels and to investigate the role of apoA-I in the anti-inflammatory effect of statin. We conducted a 6-month, prospective, randomized, open-

label study in which we assigned hypercholesterolemic patients to a pitavastatin group (n = 52; 2 mg/day) or an atorvastatin group (n = 52; 10 mg/day) to investigate the effects of these two statins on the serum apoA-I levels and serum high-sensitivity C-reactive protein (hs-CRP) levels. There were no significant differences between the two groups in the changes in the low-density lipoprotein cholesterol, high-density lipoprotein cholesterol (HDL-C), or hs-CRP levels, but the change in apoA-I in the pitavastatin group was significantly greater than in the atorvastatin group (5.3 vs. 1.4 %; p = 0.0001). A stepwise regression analysis revealed that the percent change in (DELTA) serum apoA-I level was an independent predictor of the DELTA serum hs-CRP (standard correlation coefficient = -0.198; p = 0.047). However, there was a significant negative correlation between the DELTA apoA-I levels and DELTA hs-CRP levels in the pitavastatin group (r = -0.283, p = 0.042), but not the atorvastatin group (r = -0.133, p = 0.356). The results suggest that the contribution of apoA-I to the reduction in serum hs-CRP levels by these two statins may be different. A decrease in hs-CRP level accompanied by an increase in apoA-I level may be involved in the pleiotropic effects of pitavastatin.

Thongtang, N., et al. (2017). "Effect of high-potency statins on cognitive function in patients with type 2 diabetes." Diabetes. Conference: 77th Scientific Sessions of the American Diabetes Association, ADA **66**(pp A60).

Statin use has been reported to be a potential risk of cognitive impairment, and too low plasma LDL level is associated with worse cognitive performance. We assessed the effect of high potency statin treatment and low plasma LDL levels on cognition. This was a randomized controlled study. Type 2 diabetic (DM) patients who had no atherosclerosis cardiovascular disease, and were taking simvastatin up to 20 mg/day (N=76) were randomized to continue using the same dosage of simvastatin (low potency statin group; LP) for 12 weeks or change to atorvastatin 40 mg/day for 6 weeks, and if tolerable increased to atorvastatin 80 mg/day for 6 weeks (high potency statin group; HP). Montreal Cognitive Assessment (MoCA) test and Trail Making Test part B (TMT) were assessed at baseline, 6 weeks, and 12 weeks, 73 patients completed the study. Mean age was 59+/-9 years, 72.6% female. Mean baseline plasma LDL level on simvastatin was 70.6 +/-14 mg/dl. There was no significant difference in mean age and plasma LDL levels at baseline between the LP (n=38) and HP group (n=35). Mean plasma LDL levels at 12 weeks were significantly lower in the HP group than in the LP group; LDL 72.8 +/- 22 mg/dl vs. 59.5 +/- 18.4 mg/dl; p=0.007. Mean MoCA score in the low potency statin group was 21.0, 22.8, and 23.7 at baseline, 6 weeks and 12 weeks, respectively while mean MoCA score in the HP group was 20.8, 22.3, and 23.7, respectively. TMT results were 118.9 seconds, 114.8 seconds, and 117.8 seconds at baseline, 6 weeks and 12 weeks, respectively in the LP group, while they were 125.5 second, 130.9 seconds, and 114.9 seconds, respectively in the HP group. There were no significant differences in MoCA score and TMT between the two groups in all 3 phases including patients with plasma LDL levels <40 mg/dl. In summary, increasing statin potency from low potency to high potency statins resulted in significant lower plasma LDL levels without causing cognitive decline.

Tikkanen, M. J., et al. (2013). "Effect of intensive lipid lowering with atorvastatin on

cardiovascular outcomes in coronary heart disease patients with mild-to-moderate baseline elevations in alanine aminotransferase levels." International Journal of Cardiology **168**(4): 3846-3852.

BACKGROUND: Statins may reduce cardiovascular (CV) morbidity in patients with mild-to-moderate elevations in liver enzyme levels. This post-hoc analysis of the IDEAL study compared intensive versus moderate statin therapy for the prevention of CV events in coronary heart disease patients with normal and elevated baseline levels of serum alanine aminotransferase (ALT).

METHODS: Cox regression analysis was used to investigate the effect of atorvastatin 80 mg/day versus simvastatin 20-40 mg/day on the risk of IDEAL study end points in patients with normal baseline ALT (defined as ALT < ULN [upper limit of normal]) versus elevated baseline ALT (ALT > ULN).

RESULTS: Of 8863 IDEAL patients with non-missing baseline ALT values, 7782 (87.8%) had an ALT < ULN and 1081 (12.2%) had an ALT > ULN. In patients with elevated baseline ALT, major CV event rates were 11.5% for simvastatin and 6.5% for atorvastatin, indicating a significant risk reduction with intensive statin therapy (hazard ratio, 0.556; 95% confidence interval, 0.367-0.842; p = 0.0056). Significant heterogeneity of treatment effect was observed for major CV events, cerebrovascular events, and major coronary events, with a trend towards treatment difference for the other outcomes, indicating a greater benefit with atorvastatin in the elevated ALT group.

CONCLUSIONS: The CV benefit of intensive lipid lowering with atorvastatin compared with a more moderate regimen with simvastatin was generally greater in patients with mildly-to-moderately elevated baseline ALT than patients with normal baseline ALT. Moderate elevations in liver enzyme levels should not present a barrier to prescribing statins, even at higher doses, in high-risk patients.

Toribio, M., et al. (2017). "Effects of pitavastatin and pravastatin on markers of immune activation and arterial inflammation in HIV." AIDS (london, england) **31**(6): 797-806.

Objective: Persistent immune activation is thought to contribute to increased cardiovascular disease risk in HIV and statins may help modulate systemic immune activation. We aimed to compare the effects of two key statins on markers of systemic immune activation and arterial inflammation in the HIV population. Design: Double-blind, active-controlled, parallel-group comparative trial performed in 45 sites. Methods: Two hundred and fifty-two antiretroviral therapy-treated HIV-infected participants with dyslipidemia were randomized (1:1) to pitavastatin 4mg daily vs. pravastatin 40mg daily in the HIV-infected patieNts and TREatment with PItavastatin vs. pravastatin for Dyslipidemia (INTREPID) trial. In this analysis of the INTREPID trial, we assessed markers of immune activation and arterial inflammation using a modified intent-to-treat population. This trial is registered with ClinicalTrials.gov (NCT01301066). Results: One hundred and twenty-six participants were randomized to receive pitavastatin and 126 to pravastatin. Ninety-nine participants in the pitavastatin group and 91 participants in the pravastatin group completed the study. Median age was 50 (45, 56) years [median (interquartile range)]. Baseline, low-density lipoprotein-cholestrol (LDL-C) was 153 (135, 171) mg/dl, log HIV-1 viral load was 1.1+/-0.2copies/ml, and CD4⁺ cell count was 580 (439, 794) cells/mul. At week 52, the pitavastatin group had a significantly greater reduction (% change) compared with pravastatin in soluble CD14

(sCD14), (-10.0 vs. 0.6%, P=0.02), oxidized LDL (oxLDL) (-26.9 vs. -17.5%, P=0.02), and lipoprotein-associated phospholipase 2 (Lp-PLA2) (-26.6 vs. -15.5%, P=0.005) (pitavastatin vs. pravastatin). Conclusion: Fifty-two weeks of pitavastatin 4mg daily (vs. pravastatin 40mg daily) led to a greater reduction in select markers of immune activation and arterial inflammation (sCD14, oxLDL, and LpPLA2) among HIV-infected participants. Further work is needed to assess whether immune-modulatory effects of pitavastatin reduce cardiovascular disease risk in HIV. Copyright (C) 2017 Wolters Kluwer Health, Inc.

Toyama, K., S. Sugiyama, et al. (2011). "Rosuvastatin combined with regular exercise preserves coenzyme Q10 levels associated with a significant increase in high-density lipoprotein cholesterol in patients with coronary artery disease." Atherosclerosis 217(1): 158-164.

BACKGROUND: Coenzyme Q10 levels are low in patients with coronary artery disease (CAD), and increasing or preserving coenzyme Q10 could be a beneficial strategy. Exercise and statins improve high-density lipoprotein cholesterol (HDL-C) levels. However, statins inhibit coenzyme Q10 biosynthesis, and the combination of statins with coenzyme Q10 supplementation increases HDL-C compared to statins alone. We compared the effects of two statins (rosuvastatin and atorvastatin) combined with exercise on coenzyme Q10 and HDL-C levels in CAD patients.

METHODS: After randomizing 28 CAD patients to rosuvastatin (n=14) and atorvastatin (n=14) groups, patients performed weekly in-hospital aerobic exercise and daily home exercise for 20 weeks. We measured serum lipids, ubiquinol, and exercise capacity.

RESULTS: Both statins equally improved exercise capacity and lowered low-density lipoprotein cholesterol and triglyceride levels. Rosuvastatin significantly increased HDL-C (rosuvastatin, +12 +/- 9 mg/dL [+30%], atorvastatin, +5 +/- 5 mg/dL [+13%], p=0.014) and apolipoprotein A1 (ApoA1) (rosuvastatin, +28.3 +/- 20.7 mg/dL, atorvastatin, +13.4 +/- 12.0 mg/dL, p=0.030) compared to atorvastatin. Atorvastatin significantly decreased serum ubiquinol (731 +/- 238 to 547 +/- 219 nmol/L, p=0.001), but rosuvastatin (680+/- 233 to 668 +/- 299 nmol/L, p=0.834) did not. There was a significant positive correlation between changes in ubiquinol and ApoA1 (r=0.518, p=0.005). Multivariate regression analysis showed that changes in ubiquinol correlated significantly with changes in ApoA1 after adjusting for age, sex, body mass index, and smoking (=0.502, p=0.008).

CONCLUSIONS: Compared to atorvastatin, rosuvastatin combined with exercise significantly preserved ubiquinol levels associated with an increase in HDL-C. Rosuvastatin with regular exercise could be beneficial for CAD patients. Copyright 2011 Elsevier Ireland Ltd. All rights reserved.

Truong, Q. A., S. A. Murphy, et al. (2011). "Benefit of intensive statin therapy in women: results from PROVE IT-TIMI 22." Circulation Cardiovascular Quality & Outcomes 4(3): 328-336.

BACKGROUND: Despite the known benefit of intensive statin therapy for reducing future cardiovascular events, its effectiveness in women has been questioned by some.

METHODS AND RESULTS: In the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial, 911 (21.9%) women and 3251 (78.1%) men were randomized to intensive statin (atorvastatin 80 mg) versus standard therapy (pravastatin 40 mg) therapy for a median duration of 2.1 years. The primary end point was death, myocardial infarction, unstable angina;

revascularization (occurring after 30 days); or stroke. Safety end points included elevations in liver function tests, creatine kinase, and myalgias/myositis. Women had a reduction in low-density lipoprotein (LDL) of 42.8% from baseline at 30 days (to a median of 60 mg/dL) in the intensive therapy arm, with 88.8% reaching the LDL goal of <100 mg/dL and 65.0% of <70 mg/dL, compared with a 16.8% reduction in LDL (to a median of 88 mg/dL) in the standard therapy arm. Women receiving intensive statin therapy had a significant 25% relative reduction over standard dose (hazard ratio, 0.75; 95% CI, 0.57 to 0.99; P=0.04) for the primary composite end point compared with a 14% reduction for men (hazard ratio, 0.86; 95% CI, 0.75 to 0.99; P=0.04; P-interaction, 0.38). No differences were observed between sexes for safety (all P-interaction >=0.11).

CONCLUSIONS: This trial provides evidence that both women and men derived benefit from intensive statin therapy after acute coronary syndrome, and thus, sex should not be a factor in determining who should be treated with intensive statin therapy.

Uemura, Y., M. Watarai, et al. (2012). "Atorvastatin 10 mg plus ezetimibe 10mg compared with atorvastatin 20 mg: impact on the lipid profile in Japanese patients with abnormal glucose tolerance and coronary artery disease." Journal of Cardiology 59(1): 50-56.

BACKGROUND: Oxidized low-density lipoprotein (LDL) cholesterol is a sensitive lipid marker for predicting atherosclerosis. Ezetimibe and statins are reported to decrease both LDL cholesterol and oxidized LDL cholesterol. This prospective randomized open-label crossover study compared combination therapy with atorvastatin plus ezetimibe versus high-dose atorvastatin monotherapy. Changes in serum lipids, including malondialdehyde-modified LDL (MDA-LDL) as a representative form of oxidized LDL cholesterol, and glucose metabolism were assessed.

METHODS AND RESULTS: The subjects were 39 Japanese patients with coronary artery disease and type 2 diabetes or impaired glucose tolerance who were taking 10 mg/day of atorvastatin (30 men and 9 women with a mean age of 67.8 years). They were randomized to a group that first received add-on ezetimibe (10 mg/day) or a group that first received atorvastatin monotherapy at a higher dose of 20 mg/day. Both treatments were given for 12 weeks each in a crossover fashion. Add-on ezetimibe significantly decreased MDA-LDL (109.0 +/- 31.9 mg/dl to 87.7 +/- 29.4 mg/dl, p=0.0009), while up-titration of atorvastatin did not. The decrease with add-on ezetimibe was significantly greater than with up-titration of atorvastatin (p=0.0006). Total cholesterol and LDL cholesterol were significantly decreased by both treatments, but the percent reduction with add-on ezetimibe was significantly greater (p<0.05). High-density lipoprotein cholesterol was significantly increased by both treatments and there was no significant difference between them. The apolipoprotein B/apolipoprotein A-I ratio and remnant-like particle cholesterol were only significantly decreased by add-on ezetimibe. Both treatments caused similar elevation of hemoglobin A(1c).

CONCLUSION: In Japanese patients with type 2 diabetes or impaired glucose tolerance and coronary artery disease, adding ezetimibe (10 mg/day) to atorvastatin (10 mg/day) significantly improved the lipid profile compared with atorvastatin monotherapy at 20 mg/day.

Wang, J., et al. (2017). "Efficacy of ezetimibe combined with atorvastatin in the treatment of carotid artery plaque in patients with type 2 diabetes mellitus complicated with coronary heart disease." International Angiology **36**(5): 467-473.

BACKGROUND: The aim of this study was to evaluate the efficacy of ezetimibe combined with atorvastatin in treatment of carotid artery plaque in patients with type 2 diabetes mellitus complicated with coronary heart disease (CHD). METHODS: A total of 100 patients with carotid atherosclerosis (CAS) confirmed by ultrasound and diagnosed with type 2 diabetes mellitus and CHD were randomly assigned to atorvastatin group (atorvastatin 20 mg/day) or combined treatment group (ezetimibe 10 mg/day and atorvastatin 20 mg/day). All those patients were followed for 12 months. Serum lipid, ALT, AST, and CK were measured before and after treatment. Ultrasonography was used to evaluate the stability of carotid artery plaques. RESULTS: After 12 months of treatment, the level of TC, TG, LDL-C, hs-CRP, FPG and HbA1c decreased in both groups compared with before treatment. TC, TG, LDL-C and hs-CRP in the combined treatment group were much lower than that in the atorvastatin group ($P<0.05$). The IMT and plaque area in the two groups were lower than that before the treatment ($P<0.05$). IMT and plaques area in the combined treatment group is much lower than that in the atorvastatin group after treatment. There was no significant difference in two groups on the level of ALT, AST, CK compared with baseline after treatment. CONCLUSIONS: The effect of combined use of atorvastatin and ezetimibe was better than atorvastatin alone, which can effectively reduce the blood lipid levels in diabetic patients with CHD and improve plaque stability. Both treatment regimens were safe and well tolerated. Copyright (C) 2017 EDIZIONI MINERVA MEDICA.

Watanabe, T., et al. (2015). "Anti-inflammatory and morphologic effects of pitavastatin on carotid arteries and thoracic aorta evaluated by integrated backscatter trans-esophageal ultrasound and PET/CT: a prospective randomized comparative study with pravastatin (EPICENTRE study)." Cardiovascular Ultrasound **13**: 17.

BACKGROUND: We sought to evaluate the effects of a strong lipophilic statin (pitavastatin) on plaque components and morphology assessed by transesophageal echocardiography (TEE) and transthoracic echocardiography (TTE), as well as plaque inflammation assessed by 18F-fluorodeoxyglucose (FDG) PET/CT in the thoracic aorta and the carotid artery. Furthermore, we compared the effects of pitavastatin with those of mild hydrophilic statin (pravastatin).

METHODS: We examined atherosclerotic plaques in the thoracic aorta by TEE and those in the carotid artery by integrated backscatter (IBS)-TTE and PET/CT. We identified the target plaque, where there was macrophage infiltration and inflammation, by strong FDG uptake in the thoracic aorta and carotid arteries and measured maximum standard uptake values (max SUV) by PET/CT. We measured the intima-media thickness (IMT) and the corrected IBS (cIBS) values in the intima-media complex by TEE and TTE at the same site of FDG accumulation by PET/CT.

RESULTS: Patients were randomly divided into two treatment groups: a pitavastatin group (PI group: n =10, 68.4+/-5.1 years) and a pravastatin group (PR group: n =10, 63.9+/-11.2 years). The same examinations were performed after six months at the same site in each patient. We used calculated target-to-background ratio (TBR) to measure max SUV of plaques and evaluated percent change of TBR. There was no significant difference in low

density lipoprotein-cholesterol, TBR, IMT and cIBS values in plaques at baseline between the PI and PR groups. After treatment, there was greater improvement in TBR, cIBS values and IMT in the PI group than the PR group.
CONCLUSIONS: The pravastatin treatment was less effective on plaque inflammation than pitavastatin treatment. This trend was the same in the carotid arteries and the thoracic aorta. Pitavastatin not only improved the atherosis as measured by IMT and cIBS values but also attenuated inflammation of plaques as measured by max SUV at the same site. The present study indicated that pitavastatin has stronger effects on the regression and stabilization of plaques in the thoracic aorta and carotid arteries compared with pravastatin.

West, A. M., J. D. Anderson, et al. (2011). "The effect of ezetimibe on peripheral arterial atherosclerosis depends upon statin use at baseline." Atherosclerosis 218(1): 156-162.
BACKGROUND: Both statins and ezetimibe lower LDL-C, but ezetimibe's effect on atherosclerosis is controversial. We hypothesized that lowering LDL-C cholesterol by adding ezetimibe to statin therapy would regress atherosclerosis measured by magnetic resonance imaging (MRI) in the superficial femoral artery (SFA) in peripheral arterial disease (PAD).
METHODS: Atherosclerotic plaque volume was measured in the proximal 15-20 cm of the SFA in 67 PAD patients (age 63 +/- 10, ABI 0.69 +/- 0.14) at baseline and annually x 2. Statin-naive patients (n=34) were randomized to simvastatin 40 mg (S, n=16) or simvastatin 40 mg+ezetimibe 10mg (S+E, n=18). Patients already on statins but with LDL-C >80 mg/dl had open-label ezetimibe 10mg added (E, n=33). Repeated measures models estimated changes in plaque parameters over time and between-group differences.
RESULTS: LDL-C was lower at year 1 in S+E (67 +/- 7 mg/dl) than S (91 +/- 8 mg/dl, p<0.05), but similar at year 2 (68 +/- 10 mg/dl vs 83 +/- 11 mg/dl, respectively). Plaque volume did not change from baseline to year 2 in either S+E (11.5 +/- 1.4-10.5 +/- 1.3 cm(3), p=NS) or S (11.0 +/- 1.5-10.5 +/- 1.4 cm(3), p=NS). In E, plaque progressed from baseline to year 2 (10.0 +/- 0.8-10.8 +/- 0.9, p<0.01) despite a 22% decrease in LDL-C.
CONCLUSIONS: Statin initiation with or without ezetimibe in statin-naive patients halts progression of peripheral atherosclerosis. When ezetimibe is added to patients previously on statins, peripheral atherosclerosis progressed. Thus, ezetimibe's effect on peripheral atherosclerosis may depend upon relative timing of statin therapy.

Yanagi, K., T. Monden, et al. (2011). "A crossover study of rosuvastatin and pitavastatin in patients with type 2 diabetes." Advances in Therapy 28(2): 160-171.
INTRODUCTION: The effects of a low dose of rosuvastatin (ROS) and pitavastatin (PIT) on lipid profiles and inflammation markers were assessed in subjects with type 2 diabetes mellitus.
METHODS: A total of 90 Japanese type 2 diabetes patients with hyperlipidemia (low-density lipoprotein cholesterol [LDL-C] >=140 mg/dL) were enrolled in this study. They were randomly assigned to four groups with open-label treatment with ROS (2.5 mg daily) or PIT (2 mg daily); two groups were sequentially treated with both drugs, with crossover of medication after 12 weeks, and the other two groups underwent treatment with either ROS or PIT for 24 weeks. The primary endpoints were the percentage changes in LDL-C,

high-density lipoprotein cholesterol (HDL-C) and triglyceride, and the LDL-C/HDL-C ratio.

RESULTS: Both ROS and PIT lowered LDL-C and triglyceride, and increased HDL-C. In particular, significantly greater reduction in LDL-C was seen with ROS (-44.1%) than with PIT (-36.9%, P<0.01) in the crossover group from ROS to PIT, and the same result was detected in the crossover group from PIT (-34.8%) to ROS (-44.7%). The ratio of LDL-C/HDL-C was significantly reduced with ROS treatment (from 3.45 to 1.85) compared with that with PIT (from 3.45 to 2.22, P<0.01). Both ROS and PIT lowered plasma levels of high-sensitivity C-reactive protein (hsCRP), tumor necrosis factor (TNF)-alpha, and plasminogen activator inhibitor-1 (PAI-1). In addition, the hsCRP level with the administration of ROS was significantly improved compared with the administration of PIT. There was no significant correlation between changes in LDL-C and hsCRP, TNF-alpha, and PAI-1 levels. ROS and PIT did not have an adverse effect on glycemic control in type 2 diabetes patients.

CONCLUSION: Therapy with both statins improved lipid profiles and reduced proinflammatory responses; however, 2.5 mg of ROS have a potent LDL-C-lowering and hsCRP-lowering effect compared with 2 mg of PIT in patients with diabetes.

Yamamoto, H., et al. (2014). "Difference in statin effects on neointimal coverage after implantation of drug-eluting stents." Coronary Artery Disease **25**(4): 290-295.

OBJECTIVE: This study was carried out to examine the difference in effects between rosuvastatin and pravastatin on neointimal formation after the placement of a drug-eluting stent (DES).

MATERIALS AND METHODS: Forty patients who underwent placement of a DES in our hospital were prospectively randomized to receive rosuvastatin (n=20) or pravastatin (n=20), and analyzed by optical coherence tomography at the chronic stage. The main outcome measure was comparison of neointimal coverage analyzed at a strut level.

RESULTS: A significant reduction in total cholesterol, low-density lipoprotein, and white blood cell count was observed during the study in the rosuvastatin group (total cholesterol, from 4.82+/-0.90 to 4.43+/-0.77 mmol/l, P=0.038; low-density lipoprotein, from 2.85+/-0.76 to 2.34+/-0.57 mmol/l, P=0.006; white blood cell count, from 5810+/-1399 to 5355+/-1257/micro l, P=0.048), but not in the pravastatin group. Although not statistically significant, C-reactive protein was lower in the rosuvastatin than in the pravastatin group at the chronic stage (1.14+/-1.21 vs 7.67+/-13.67 mg/l, P=0.051). Malapposed and uncovered struts were significantly less frequent in the rosuvastatin group than in the pravastatin group (malapposed, 0.06 vs 0.60%, P<0.001; uncovered, 6.49 vs 11.29%, P<0.001). The difference in uncovered struts was maintained even when stent types were analyzed separately (everolimus-eluting stent, 4.81 vs 6.21%, P=0.007; sirolimus-eluting stent, 14.40 vs 20.86%, P<0.001). Comparison of neointimal thickness between the rosuvastatin and the pravastatin groups showed inconsistent results depending on the stent types analyzed.

CONCLUSION: Compared with pravastatin, the use of rosuvastatin resulted in lower frequency of uncovered and malapposed struts after the placement of a DES, which might be mediated through improved inflammatory and lipid profiles.

Yokoi, H., R. Nohara, et al. (2014). "Change in carotid intima-media thickness in a high-risk group of patients by intensive lipid-lowering therapy with rosuvastatin: subanalysis of the JART study." International Heart Journal **55**(2): 146-152.

Carotid intima-media thickness (IMT), a measure of atherosclerosis, is modulated by multiple risk factors. Accordingly, comprehensive control of risk factors is indispensable for management of atherosclerosis. In this study, as a posthoc analysis of the JART Study we planned two analyses. In the main analysis, we evaluated the effect of intensive lipid-lowering therapy with rosuvastatin on carotid IMT in high-risk patients. We also evaluated efficacy in the presence or absence of each risk factor using the full analysis population in the JART Study. Patients with low-density lipoprotein cholesterol (LDL-C) > 140 mg/dL and max-IMT > 1.1 mm were randomized to rosuvastatin or pravastatin therapy for 12 months. Dosages were allowed to increase to 10 mg/day and 20 mg/day to achieve LDL-goals (aggressive goals for rosuvastatin group and guideline goals for pravastatin group). For the main analysis, we assessed 200 high-risk patients (105 in the rosuvastatin group), as category III or secondary prevention according to the Japan Atherosclerosis Society guideline 2007, whereas we assessed 289 patients in the other analysis. Rosuvastatin significantly slowed the percentage change in mean-IMT at 12 months compared with pravastatin (1.40 + 10.03% versus 6.43 + 13.77%, P = 0.005). LDL-C was reduced by 48.1% in the rosuvastatin group and 27.9% in the pravastatin group. The rate of achieving the LDL-C goal was significantly greater in the rosuvastatin group compared with the pravastatin group (P < 0.001). Rosuvastatin slowed the change in mean-IMT in the presence of every risk factor. Thus, intensive lipid-lowering therapy reduced progression of carotid IMT in high-risk patients.