

Drug Class Review

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

Preliminary Scan Report

August 2014

Last Report: Update #5 (November 2009)

The purpose of Drug Effectiveness Review Project reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. Reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Scan conducted by:

Brittany Holzhammer, MPH
Kim Peterson, MS
Ryan Stoner, MA

Drug Effectiveness Review Project
Marian McDonagh, PharmD, Principal Investigator

Pacific Northwest Evidence-based Practice Center
Roger Chou, MD, Director
Marian McDonagh, PharmD, Associate Director

Oregon Health & Science University

Copyright © 2014 by Oregon Health & Science University
Portland, Oregon 97239. All rights reserved.



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. 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 rule in favor of a full update. The literature search for this report focuses only on new randomized controlled trials and comparative effectiveness reviews, and actions taken by the U.S. Food and Drug Administration (FDA) since the last report. Other important studies, including observational studies, could exist.

Date of Last Update Report

Update #5, November 2009 (searches through June 2009)

Date of Last Preliminary Update Scan Report

August 2013

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, pain care specialists, 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 the 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?
4. 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)?
5. 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)?
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 the general population of children or adults?
7. 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

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).
- Both children and adults will be included.
 - Children with familial hypercholesterolemia (homozygous or heterozygous) will be included.
- Exclusions: Adults with rare, severe forms of hypercholesterolemia (LDL-c \geq 250mg/dl).

Interventions

Table 1. Individual statins

Active ingredient	Brand name
Atorvastatin	Lipitor
Fluvastatin	Lescol
Fluvastatin extended release	Lescol XL
Lovastatin	Generic
Lovastatin extended release	Altoprev*
Pitavastatin	Livalo
Pravastatin	Pravachol
Rosuvastatin	Crestor
Simvastatin	Zocor

Table 2. Fixed-dose combination products containing a statin

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

*Not available in Canada

Shading indicates new drugs identified since the last update report

Exclusions: Caduet (atorvastatin; amlodipine)

Study designs

- For assessment of effectiveness, controlled clinical trials and systematic reviews.
- For assessment of harms, controlled clinical trials, observational studies, and systematic reviews.

Comparators: Effectiveness and harms of individual statins

- For Key Questions 1 and 2, head-to-head trials comparing one statin to another.
- For other key questions, trials comparing a statin to placebo or another active comparator.

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, placebo, or another active comparator.

Exclusions: Trials comparing a fixed-dose combination product to the product's individual components given separately (co-administration).

Effectiveness outcomes

- Reduction in nonfatal MI, CHD, mortality (CHD and all-cause), stroke, and need for revascularization (including coronary artery bypass grafting, angioplasty and coronary stents)
- LDL-c lowering ability
- HDL-c raising ability

Harms outcomes

- Overall adverse events
- Withdrawals due to adverse events
- Serious adverse events
- Specific adverse events (including, but not limited to, hepatotoxicity, myopathy, rhabdomyolysis, renal toxicity, myalgia)

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE and Ovid MEDLINE In-Process & Other Non-Indexed Citations from August 2013 to July 25, 2014 using terms for included drugs. We also searched the FDA website (<http://www.fda.gov/medwatch/safety.htm>) for identification of new drugs, indications, and safety alerts. 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”).

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

New Drugs

Identified in this Preliminary Update Scan

None

Identified in previous Preliminary Update Scans

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

Juvisync™: FDA approved a new fixed dose combination product comprised of sitagliptin and simvastatin on 10/7/2011 that is indicated in patients for whom treatment with both sitagliptin and simvastatin is appropriate. *Note: Juvisync has since been discontinued.*

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

New Indications

Identified in this Preliminary Update Scan

None

Identified in previous Preliminary Update Scans

February 2010: New indication for rosuvastatin (Crestor®) for the primary prevention of cardiovascular disease (risk reduction of MI, stroke, and arterial revascularization procedures in patients without clinically evident CHD, but with multiple risk factors), based on the results of Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER).

New Safety Alerts

Identified in this Preliminary Update Scan

None

Identified in previous Preliminary Update Scans

UPDATED 12/15/2011: FDA notified the public that it has revised the dose limitation for simvastatin from 10 mg to 20 mg when it is co-administered with the cardiac drug amiodarone. The simvastatin drug labels (Zocor and generics, Vytorin) have been updated to reflect this correction.

Posted 06/08/2011: FDA notified healthcare professionals that it is recommending limiting the use of the highest approved dose of the cholesterol-lowering medication simvastatin (80 mg) because of increased risk of muscle damage. Patients taking simvastatin 80 mg daily have an increased risk of myopathy compared to patients taking lower doses of this drug or other drugs in the same class. This risk appears to be higher during the first year of treatment, is often the result of interactions with certain medicines, and is frequently associated with a genetic predisposition toward simvastatin-related myopathy. The most serious form of myopathy, called rhabdomyolysis, can damage the kidneys and lead to kidney failure which can be fatal. FDA is requiring changes to the simvastatin label to add new contraindications (should not be used with certain medications) and dose limitations for using simvastatin with certain medicines.

Posted 03/19/2010: FDA notified healthcare professionals and patients that, based on review of data from a large clinical trial and other sources, there is an increased risk of muscle injury in patients taking the highest approved dose of the cholesterol-lowering medication, Zocor (simvastatin) 80 mg, compared to patients taking lower doses of simvastatin and possibly other drugs in the "statin" class. FDA is also reviewing data from other clinical trials, observational studies, adverse event reports, and data on prescription use of simvastatin to better understand the relationship between high-dose simvastatin use and muscle injury.

Comparative Effectiveness Reviews

Reviews identified in this Preliminary Update Scan

In the present scan, we identified one new comparative effectiveness review. This review is an update of the 2009 AHRQ Comparative Effectiveness Review on lipid-modifying agents and was completed in February 2014. The citation for this updated review is listed below and the structured abstract is provided in Appendix A.

1. Monroe AK, Gudzone KA, Sharma R, Chelladurai Y, Ranasinghe PD, Ansari MT, Robinson KA. Combination Therapy Versus Intensification of Statin Monotherapy: An Update. Comparative Effectiveness Review No. 132. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. 290-2012-00007-I.) AHRQ Publication No. 14-EHC013-EF. Rockville, MD: Agency for Healthcare Research and Quality; February 2014. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Reviews identified in previous Preliminary Update Scans

Two comparative effectiveness reviews were identified in previous preliminary update scans published since the last update report. The citations for these reviews are listed below and the research questions and research messages are provided in Appendix A.

2. Lipid Lowering Agents for Stroke Prevention: A Review of the Clinical Evidence, Safety and Guidelines. Canadian Agency for Drugs and Technologies in Health. March 2012. <http://www.cadth.ca/media/pdf/htis/mar-2012/RC0331%20Lipid%20Lowering%20Agents%20Final.pdf>.
3. Statin Therapy in Adults with Diabetes: Clinical Efficacy. Canadian Agency for Drugs and Technologies in Health. September 2011. http://www.cadth.ca/media/pdf/htis/sept-2011/RB0419_Statins_final.pdf.

Controlled Clinical Trials

Trials identified in this Preliminary Update Scan

Medline searches for this scan resulted in 195 citations. Of those, there are 28 potentially relevant new trials, including 13 head-to-head trials and 15 placebo-controlled trials.

Trials identified since the most recent Full Report

Since the most recent full report, we have identified a total of 72 new head-to-head trials and 43 new placebo-controlled trials. A list of head-to-head trials and a summary of their characteristics is included in Table 3 and corresponding abstracts are available in Appendix B.

Six head-to-head trial publications reported health outcomes such as cardiovascular mortality, hospitalization for cardiovascular morbidity, recurrent cardiovascular events, myocardial infarction, unstable angina, revascularization, and stroke; five of which are secondary publications of previously included trials (see Table 3). The one new unique trial with health outcomes was evaluating the use of statins given immediately prior to percutaneous coronary interventions. Sixty-six head-to-head trials reported intermediate outcomes such as changes to LDL-C and/or HDL-C levels, 12 that are secondary publications of other trials. It is not clear if all of these have been included in the last DERP report based on the abstracts.

Table 3. Potentially relevant head-to-head trials reporting health and/or lipid outcomes

Author Year	Comparison	Population	Outcome	Secondary analysis of a previously included trial?
Long-term outcomes				
Brouwers 2011	Pravastatin 40 mg vs fosinopril 20 mg	Microalbuminuria	Cardiovascular mortality and hospitalization for cardiovascular morbidity	PREVEND IT
Gibson 2009	Atorvastatin 80 mg vs pravastatin 40 mg	Acute coronary syndrome, undergoing PCI	Major adverse cardiovascular events	PROVE-IT
Murphy 2009	Atorvastatin 80 mg vs pravastatin 40 mg	Acute coronary syndrome	Recurrent cardiovascular events	PROVE-IT
Truong 2011	Atorvastatin 80 mg vs simvastatin 20 to 40 mg	Women	Death, MI, unstable angina, revascularization (occurring after 30 days), or stroke	PROVE IT-TIMI 22
Pedersen 2010	Atorvastatin 80 mg vs simvastatin 20 to 40 mg	Post-MI	Cardiovascular events after 5 years	IDEAL
Sardella 2013	(1) Pre-PCI reloading dose of rosuvastatin 40 mg vs. (2) Pre-PCI reloading dose of atorvastatin 80 mg vs. (3) Chronic statin therapy without reloading	Patients with stable angina undergoing elective PCI	Occurrence of major cardiac and cerebrovascular events	--
Intermediate outcomes (lipids)				
Araujo 2010	Simvastatin 80 mg vs. simvastatin 10 mg + ezetimibe 10 mg	Hypercholesterolemia	LDL-C	--
Arimura 2012	Atorvastatin 10 mg vs. atorvastatin/ezetimibe 10/10 mg	Patients with stable angina undergoing coronary stent implantation	LDL-C	--
Aslangul 2010	Rosuvastatin 10 mg vs. pravastatin 40 mg	HIV-1 infected patients treated with a boosted protease inhibitor; dyslipidemia	LDL-C	--
Averna 2011	Switching to ezetimibe/simvastatin 10/20 mg vs. rosuvastatin 10 mg	High-risk hypercholesterolemic patients with and without metabolic syndrome	LDL-C	Post hoc analysis
Azar 2011	Atorvastatin 40 mg + ezetimibe 10 mg vs. atorvastatin 40 mg	Patients with stable coronary artery disease or coronary	LDL-C	--

		artery disease equivalent (diabetes, stroke, or peripheral vascular disease)		
Backes 2012	Rosuvastatin 80 mg vs. atorvastatin 10 mg	Dyslipidemia with LDL-C > 100 mg/dl and triglycerides < 200 mg/dl	LDL-C	--
Bahadir 2009	Rosuvastatin 10 mg vs. atorvastatin 20 mg vs. simvastatin 40 mg vs. pravastatin 40 mg	Hypercholesterolemic patients with metabolic syndrome	LDL-C	--
Bardini 2010	Ezetimibe 10 mg + simvastatin 20 mg vs. simvastatin 40 mg	Adult patients with type 2 diabetes mellitus and CHD	LDL-C	--
Bays 2013	Study Period I: (1) Atorvastatin 10 mg + ezetimibe 10 mg vs. (2) Atorvastatin to 20 mg vs. (3) Rosuvastatin 10 mg Study Period II: (1) Atorvastatin 10 mg + ezetimibe 10 mg vs. (2) Atorvastatin 20 mg + ezetimibe 10 mg or uptitration of atorvastatin to 40 mg vs. (3) Switching to atorvastatin 20 mg + ezetimibe 10 mg or uptitration of rosuvastatin to 20 mg	Primary hypercholesterolemia patients with high atherosclerotic cardiovascular disease risk and LDL-C > 100 and < 160 mg/dl	LDL-C reduction and attainment of LDL-C targets < 100 or < 70 mg/dl	--
Bellia 2010	Rosuvastatin 20 mg vs. simvastatin 20 mg	Middle-aged patients with type 2 diabetes and mild untreated dyslipidemia	LDL-C	--
Boh 2011	Generic (10-20 mg) or reference atorvastatin (20-40 mg)	LDL-C > 3 mmol/L and increased coronary risk	Attainment of target LDL-C of 2.99 mmol/L	--
Eriksson 2011a	Pitavastatin 4 mg vs. simvastatin 40 mg	Primary hypercholesterolemia or combined dyslipidemia and at least two CHD risk factors	Change in LDL-C from baseline	--
Eriksson 2011b	Pitavastatin 4 mg vs. simvastatin 80 mg	Dyslipidemic patients at high risk of CHD	Attainment of NCE target LDL-C	Extension of Eriksson 2011a
Florentin 2011	Simvastatin 40 mg vs. simvastatin/ezetimibe 10/10 mg	Primary hypercholesterolemia	LDL-C	--
Foody 2010	Ezetimibe/simvastatin 10/20 mg vs. atorvastatin 10 or 20 mg	Hypercholesterolemic patients ≥ 65 years with or without	LDL-C	--

	vs. ezetimibe/simvastatin 10/40 mg vs. atorvastatin 40 mg	cardiovascular disease		
Gumprecht 2011	Pitavastatin 4 mg vs. atorvastatin 20-40 mg	Type 2 diabetes mellitus and combined (mixed) dyslipidemia	LDL-C	--
Hall 2009	Rosuvastatin 10 mg vs. simvastatin 40 mg	Hyperlipidemia	LDL-C	--
Han 2012	Pitavastatin 2-4 mg vs. atorvastatin 10-20 mg	Hypercholesterolemic patients with elevated serum alanine transaminase	LDL-C	--
Her 2010	Atorvastatin 20 mg vs. rosuvastatin 10 mg vs. atorvastatin/ezetimibe 5/5 mg	Hypercholesterolemia	LDL-C	--
Hing Ling 2012	Ezetimibe/simvastatin 10/40 mg vs. atorvastatin 40 mg	High cardiovascular risk patients with primary hypercholesterolemia	Percent change in LDL-C	--
Hongo 2011	Rosuvastatin 2.5-5 mg vs. fluvastatin 20-40 mg	Japanese patients with dyslipidemia	LDL/HDL ratio	--
Jimenez 2013	(1) Switching to ezetimibe/simvastatin 10/20 mg vs. (2) Doubling baseline statin dose (to simvastatin 40 mg or atorvastatin 20 mg) vs. (3) Switching to rosuvastatin 10 mg	Diabetics with and without metabolic syndrome	LDL-C	Post hoc analysis
Kim 2013	Two formulations of atorvastatin 20 mg	Primary hypercholesterolemia with LDL-C > 100 mg/dl	Percent change in LDL-C	--
Koksal 2011	Atorvastatin 20 mg vs. rosuvastatin 10 mg	Type 2 diabetes mellitus with LDL-C > 100 mg/dl	LDL-C	--
Kurogi 2013	Pitavastatin 2-4 mg vs. atorvastatin 10-20 mg	Stable coronary artery disease, hypercholesterolemia, and hypo-HDL-cholesterolemia (HDL-C < 50mg/dl)	Percent changes in HDL-C	--
Lablanche 2010	Rosuvastatin 20 mg vs. atorvastatin 80 mg	Acute coronary syndrome	LDL-C	--
Lee 2011	Atorvastatin 20 mg vs. atorvastatin/ezetimibe 5/5 mg	Hypercholesterolemia	LDL-C	--
Lee 2012a	Atorvastatin 20 mg vs. rosuvastatin 10 mg	Statin naïve patients with mild coronary atherosclerotic plaques	Lipid levels	ARTMAP
Lee 2012b	Atorvastatin 20 mg vs.	Combined	LDL-C, HDL-C	--

	atorvastatin/ezetimibe 5/5 mg	hyperlipidemia		
Lee 2013	Ezetimibe/simvastatin 10/20 mg vs. atorvastatin 20 mg	Korean patients with type 2 diabetes mellitus and LDL-C > 100 mg/dl	LDL-C, HDL-C	--
Liu 2011	Rosuvastatin 10 mg vs. atorvastatin 20 mg	Stable atherosclerosis	LDL-C	--
Moreira 2014	Rosuvastatin 40 mg vs. ezetimibe/simvastatin 10/40 mg	Hyperlipidemic subjects	Electronegative LDL	--
Moutzouri 2013	Simvastatin/ezetimibe 10/10 mg vs. simvastatin 40 mg vs. rosuvastatin 10 mg	Dyslipidemia	Lipid levels	--
Murrow 2012	Pravastatin 80 mg vs. atorvastatin 10 mg	Hyperlipidemia and metabolic syndrome and/or diabetes	LDL-C	--
Nicholls 2011	Atorvastatin 80 mg vs. rosuvastatin 40 mg	Coronary disease	LDL-C	--
Nohara 2012	Rosuvastatin 5-10 mg vs. pravastatin 10-20 mg	Adults with hypercholesterolemia and max carotid intima-media thickness \geq 1.1 mm	LDL-C/HDL-C ratio	--
Olsson 2011	Simvastatin 20 or 40 mg vs. atorvastatin 80 mg	CVD	Attainment of LDL- C goals of 2.5 or 2.0 mmol/L	IDEAL
Ose 2009	Pitavastatin 2 mg vs. pitavastatin 4 mg vs. simvastatin 20 mg vs. simvastatin 40 mg	Primary hypercholesterolemia or combined dyslipidemia	LDL-C	--
Padhy 2013	Ezetimibe 10 mg + atorvastatin 10 mg vs. atorvastatin 10 mg monotherapy	Indian patients with dyslipidemia	LDL-C; attainment of NCE target for LDL-C	--
Park 2010	Rosuvastatin 10 mg vs. atorvastatin 10 mg	Korean patients with nondiabetic metabolic syndrome	LDL-C	--
Pesaro 2012	Ezetimibe/simvastatin 10/20 mg vs. simvastatin 80 mg	Coronary artery disease	LDL-C	--
Pitt 2012	Rosuvastatin 20 mg vs. rosuvastatin 40 mg vs. atorvastatin 80 mg	Adults with coronary artery disease	LDL-C	LUNAR
Polis 2009	Ezetimibe/simvastatin (10/10, 10/20, 10/40, 10/80 mg) vs. atorvastatin (10, 20, 40, 80 mg) or rosuvastatin (10, 20, 40 mg)	Diabetes mellitus, metabolic syndrome, or neither condition	LDL-C	Post hoc analysis
Puccetti 2011	Atorvastatin 20 mg vs. rosuvastatin 10 mg	Hypercholesterolemia	LDL-C	--
Puri 2013	Rosuvastatin 40 mg vs. atorvastatin 80 mg	Patients with coronary atherosclerosis with	LDL-C, HDL-C	SATURN

		and without diabetes		
Ramos 2011	Rosuvastatin 40 mg + fiber 25 mg vs. rosuvastatin 40 vs. simvastatin 40 mg + ezetimibe 10 mg + fiber 25 mg vs. simvastatin 40 mg + ezetimibe 10 mg	Primary hypercholesterolemia	LDL-C, HDL-C	--
Robinson 2011	Ezetimibe/simvastatin (10/20 and 10/40 mg) vs. atorvastatin (10, 20, 40 mg)	Metabolic syndrome	LDL-C	VYMET
Robinson 2013	Ezetimibe/simvastatin (10/20 and 10/40 mg) vs. atorvastatin (10, 20, 40 mg)	Metabolic syndrome patients with and without diabetes	LDL-C, HDL-C	VYMET
Rosen 2013	(1) Switching to ezetimibe/simvastatin 10/20 mg vs. (2) Doubling run-in statin dose to simvastatin 40 mg or atorvastatin 20 mg vs. (3) Switching to rosuvastatin 10 mg	Subjects with cardiovascular disease and diabetes	Percentage change in LDL-C, percentage of patients achieving LDL-C < 70 mg/dl	--
Rotella 2010	Ezetimibe/simvastatin 10/20 mg vs. simvastatin 40 mg	CHD and/or type 2 diabetes mellitus	LDL-C	--
Rudofsky 2012	Simvastatin 80 mg vs. simvastatin/ezetimibe 10/10 mg vs. placebo	Type 2 diabetes	LDL-C	--
Ruggenenti 2010	Simvastatin/ezetimibe 40/10 mg vs. simvastatin 40 mg	Type 2 diabetes	LDL-C	--
Saku 2011	Atorvastatin 10 mg vs. rosuvastatin 2.5 mg vs. pitavastatin 2 mg	Patients with risk factors for coronary artery disease and elevated LDL-C	LDL-C	--
Sansanayudh 2010	Pitavastatin 1 mg vs. atorvastatin 10 mg	Hypercholesterolemia	LDL-C	--
Sasaki 2013	Pravastatin 10 mg vs. atorvastatin 10 mg	Men aged > 20 years; postmenopausal women with LDL-C > 140 mg/dl, HDL-C < 80 mg/dl, and triglycerides < 500 mg/dl and who had glucose intolerance	LDL-C, HDL-C	--
Scheffer 2013	Atorvastatin 10 mg vs. simvastatin 40 mg	Statin-naïve patients with diabetes mellitus and/or obesity and/or hypertension	LDL-C	--
Shimabukuro 2011	Pitavastatin 2 mg vs. atorvastatin 10 mg	Type 2 diabetes with hypercholesterolemia and/or triglyceridemia	LDL-C, HDL-C	--

Stender 2013a	Pitavastatin (1, 2, 4 mg) vs. pravastatin (10, 20, 40 mg)	Elderly patients with primary hypercholesterolemia or combined (mixed) dyslipidemia	LDL-C	--
Stender 2013b	Pitavastatin (2, 4, 8 mg)	Elderly patients with primary hypercholesterolemia or combined (mixed) dyslipidemia	LDL-C	Companion to Stender 2013a
Toyama 2011	Rosuvastatin 2.5-20 mg vs. atorvastatin 10-40 mg	Coronary artery disease	HDL-C	--
Uemura 2012	Atorvastatin/ezetimibe 10/10 mg vs. atorvastatin 20 mg	Japanese patients with abnormal glucose tolerance and coronary artery disease	LDL-C	--
Undas 2011	Simvastatin 40 mg + ezetimibe 10 mg vs. simvastatin 40 mg + placebo	Acute coronary syndrome	LDL-C	--
West 2011	Statin naïve: Simvastatin 40 mg vs. simvastatin 40 mg + ezetimibe 10 mg Statin experienced: Addition of ezetimibe 10 mg	Patients with peripheral arterial disease	LDL-C	--
Yanagi 2011	Rosuvastatin 2.5 mg vs. pitavastatin 2 mg	Japanese type 2 diabetes patients with hyperlipidemia	LDL-C, HDL-C	--
Yokoi 2014	Rosuvastatin 5-10 mg vs. pravastatin 10-20 mg	Patients with LDL-C > 140 mg/dl and max carotid intima-media thickness > 1.1 mm	LDL-C of 80 mg/dl for primary prevention or 70 mg/dl for secondary prevention with rosuvastatin; LDL-C complying with JASGL2007 guideline for pravastatin	JART
Yoshida 2013	Pitavastatin 2 mg vs. atorvastatin 10 mg	Hypercholesterolemia	Lipoprotein oxidative biomarkers	--

PCI = percutaneous coronary intervention, JASGL2007 = Japan Atherosclerosis Society guideline 2007
 Shading indicates trials identified in the present scan

Placebo-controlled, usual care-controlled or no statin-controlled trials reporting health or lipid outcomes by statin or fixed-dose combination

Placebo-controlled trials are listed below by statin or fixed-dose combination drug of study. Twenty-three placebo-controlled trials reported subgroup or secondary analyses from trials previously included in the DERP statins report. One placebo-controlled trial (Koh 2013) compared rosuvastatin 10 mg and pravastatin 40 mg to placebo and to each other and is, therefore, listed under both the rosuvastatin and pravastatin drug headings below. Abstracts for placebo-controlled trials are available upon request.

Atorvastatin

- Amarenco 2010 (companion to SPARCL)
- Athyros 2010 (companion to GREACE)
- Athyros 2013 (companion to GREACE)
- Chapman 2011
- Colhoun 2009 (companion to CARDS)
- Collier 2011 (companion to ASCOT)
- Dohi 2010
- Dohi 2011 (companion to ESTABLISH)
- Goldstein 2009 (companion to SPARCL)
- Hong 2013
- Mulders 2012
- Sever 2011 (companion to ASCOT-LLA)

Fluvastatin

- Ostadal 2010

Lovastatin

- Kendrick 2010 (companion to AFCAPS)
- Koenig 2011 (companion to JUPITER)
- Koh 2013
- Leoncini 2014
- Luo 2013
- Mora 2010 (companion to JUPITER)
- Ridker 2009 (companion to JUPITER)
- Ridker 2012 (companion to JUPITER)
- Talavera 2013

Pitavastatin

- Takano 2013

Pravastatin

- Cueto-Manzano 2013
- Kim 2013a
- Koh 2013
- Lloyd 2013 (companion to PROSPER)
- Margolis 2013 (companion to ALLHAT-LLT)
- Rahman 2013 (companion to ALLHAT)
- Ryu 2011

Rosuvastatin

- Albert 2011 (companion to JUPITER)
- Avis 2010
- Eckard 2014
- Everett 2010 (companion to JUPITER)
- Glynn 2010 (companion to JUPITER)
- Holdaas 2011 (companion to AURORA)
- Hsia 2011 (companion to JUPITER)
- Kennedy 2011

Simvastatin

- Cash 2013
- Garcia-de-la-Puente 2009
- Heart Protective Study Collaborative 2011 (companion to HPS)
- Kim 2013b

Simvastatin + ezetimibe

- Baigent 2011 (companion to SHARP)

Shading indicates trials identified in the present scan

Summary

Since the last full report, there has been one new statin approved (pitavastatin) and two new fixed-dose combination products approved. Rosuvastatin received approval for use in primary prevention of coronary artery disease, and warnings about dose limitations for simvastatin were issued. However, there were no new drugs, indications, or boxed warnings identified since the last scan. Since the last full report, there are three comparative effectiveness reviews published by other organizations that may be relevant to this DERP topic; one published in 2014.

Since the last scan, there are a total of 72 new head-to-head trial publications; 13 in the present scan. However, only six of these report health outcomes, with the rest reporting intermediate lipid outcomes. Additionally, only one of the publications with health outcomes is a new, unique trial; the others are secondary publications of data from trials already included in the report. Twelve of 66 trials reporting lipid outcomes were secondary analyses.

APPENDIX A. NEW COMPARATIVE EFFECTIVENESS REVIEWS (N = 3)

Shading indicates comparative effectiveness reviews identified in the present scan

1. Monroe AK, Gudzone KA, Sharma R, Chelladurai Y, Ranasinghe PD, Ansari MT, Robinson KA. Combination Therapy Versus Intensification of Statin Monotherapy: An Update. Comparative Effectiveness Review No. 132. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. 290-2012-00007-I.) AHRQ Publication No. 14-EHC013-EF. Rockville, MD: Agency for Healthcare Research and Quality; February 2014. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Structured Abstract

Objective. To assess the benefits and harms of combination of statin and other lipid-modifying medication compared to intensification of statin monotherapy. This is an update to a 2009 review.

Data sources. The search for the prior review included MEDLINE® from 1966 to May 2009, Embase® from 1980 to May 2009, and the Cochrane Library to the third quarter of 2008. Additional searches of MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) from May 2008 to July 2013 were conducted for the update.

Review methods. Paired investigators independently screened search results to assess eligibility. Investigators abstracted data sequentially and assessed risk of bias independently. Investigators graded the strength of evidence (SOE) as a group.

Results. All evidence for clinical outcomes (mortality, acute coronary events, and revascularization procedures) were graded as insufficient when comparing lower potency combination therapy with higher potency statin monotherapy. Results of effects on surrogates—low-density lipoprotein (LDL-c) and high-density lipoprotein (HDL-c)—and on serious adverse events are summarized below:

Bile acid sequestrants (BAS): There was moderate SOE from four trials that a low-potency statin combined with a BAS lowered LDL-c up to 14 percent more than mid-potency statin monotherapy.

Ezetimibe: Moderate SOE from 11 trials favors mid-potency statin with ezetimibe for lowering LDL-c, with reduction up to 18 percent more compared to high-potency statin monotherapy among general populations. Low SOE from 11 trials favors mid-potency statin with ezetimibe for raising HDL-c, with increase up to 6 percent more compared to high-potency statin monotherapy.

Fibrates: There is insufficient evidence to compare combination therapy with fibrate and statin to intensification of statin monotherapy regardless of statin potency.

Niacin: There is insufficient evidence to compare combination therapy with niacin and statin to intensification of statin monotherapy on lowering LDL-c, regardless of statin potency. Moderate SOE from three trials found that low-potency statin with niacin raises HDL-c up to 27 percent more than mid-potency statin monotherapy.

Omega-3 fatty acids: No relevant trials were found.

Conclusions. Although many studies looked at intermediate outcomes, few studies addressed the question of which approach produces better clinical outcomes. Combination of statin with ezetimibe or bile acid sequestrant lowered LDL-c better than intensification of statin monotherapy, but evidence for clinical outcomes (mortality, acute coronary events, and revascularization procedures) was insufficient across all potency comparisons for all combination therapy regimens. Additional studies evaluating long-term clinical benefits and vii harms are needed to better inform clinical decisionmaking, patient choice, and clinical practice guidelines.

2. Lipid Lowering Agents for Stroke Prevention: A Review of the Clinical Evidence, Safety and Guidelines. Canadian Agency for Drugs and Technologies in Health. March 2012. <http://www.cadth.ca/media/pdf/htis/mar-2012/RC0331%20Lipid%20Lowering%20Agents%20Final.pdf>.

RESEARCH QUESTIONS

1. What are the evidence-based guidelines and recommendations regarding the use of lipid lowering agents for stroke prevention in frail elderly patients?
2. What is the clinical effectiveness of lipid lowering agents for stroke prevention in frail elderly patients?
3. What is the clinical evidence on the safety and harms of using lipid lowering agents for stroke prevention in frail elderly patients?
4. What is the clinical evidence on the safety and harms of discontinuing lipid lowering agents in frail elderly patients?

KEY MESSAGE

There is evidence to suggest that statins are safe and effective in reducing the risk of stroke in elderly patients. Discontinuation of statin therapy was an independent predictor of one-year all-cause mortality.

3. Statin Therapy in Adults with Diabetes: Clinical Efficacy. Canadian Agency for Drugs and Technologies in Health. September 2011. http://www.cadth.ca/media/pdf/htis/sept-2011/RB0419_Statins_final.pdf.

RESEARCH QUESTION(S)

1. What is the clinical efficacy of statin therapy versus placebo or standard care in adults with diabetes and without a history of cardiovascular diseases?
2. What is the clinical efficacy of statin therapy versus placebo or standard care in adults with diabetes and with a history of cardiovascular diseases?

KEY MESSAGE

Evidence suggests that statin therapy is an efficient therapy when compared with placebo or standard of care in adults with diabetes with or without a history of cardiovascular diseases.

APPENDIX B. HEAD-TO-HEAD TRIALS OF HEALTH AND LIPID OUTCOMES (N=72)

Shading indicates trials identified in the present scan

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. Copyright 2012 Japanese College of Cardiology. Published by Elsevier Ltd. All rights reserved.

Aslangul, E., L. Assoumou, et al. (2010). "Rosuvastatin versus pravastatin in dyslipidemic HIV-1-infected patients receiving protease inhibitors: a randomized trial." *AIDS* **24**(1): 77-83.

BACKGROUND: HIV infection and its treatment with protease inhibitors, especially when boosted with ritonavir, can cause lipid disorders. Statins, with the exception of fluvastatin, pravastatin and rosuvastatin, interact with protease inhibitor metabolism via CYP450. Pravastatin is recommended for patients with protease inhibitor-associated dyslipidemia. Rosuvastatin is the statin most effective on low-density lipoprotein cholesterol (LDL-c) in non-HIV patients. **METHODS:** HIV-1-infected patients treated with boosted protease inhibitor were randomized to receive either rosuvastatin 10 mg/day or pravastatin 40 mg/day for dyslipidemia (LDL-c >4.1 mmol/l and triglycerides <8.8 mmol/l). The percentage change in LDL-c, triglyceride and high-density lipoprotein-cholesterol levels, measured in a central laboratory, was determined after 45 days of statin treatment. **RESULTS:** Eighty-eight patients were randomized and 83 took the study drugs, 41 rosuvastatin and 42 pravastatin. The median duration of prior antiretroviral treatment was 9 years. At baseline, the median LDL-c level was 4.93 mmol/l, the triglyceride level 2.29 mmol/l, and the high-density lipoprotein-cholesterol level 1.27 mmol/l. The median percentage changes in the rosuvastatin and pravastatin arms were -37 and -19% for LDL-c ($P < 0.001$), respectively, and -19 and -7% for triglycerides ($P = 0.035$), respectively. The change in the high-density lipoprotein-cholesterol level was not significantly different between the two arms. None of the four severe adverse events was attributed to the statins; in particular, there were no renal, hepatic or muscular events. **CONCLUSION:** Rosuvastatin 10 mg/day was more effective than pravastatin 40 mg/day on LDL-c and triglyceride levels in HIV-1-infected patients receiving a boosted protease inhibitor.

Averna, M., L. Missault, et al. (2011). "Lipid-altering efficacy of switching to ezetimibe/simvastatin 10/20 mg versus rosuvastatin 10 mg in high-risk patients with and without metabolic syndrome." *Diabetes & Vascular Disease Research* **8**(4): 262-270.

Metabolic syndrome (MetS) is a clustering of atherosclerotic coronary heart disease risk factors. This post-hoc analysis compared the effects of switching to ezetimibe/simvastatin 10/20 mg or rosuvastatin 10 mg in a cohort of 618 high-risk hypercholesterolaemic patients with ($n=368$) and without ($n=217$) MetS who had previously been on statin monotherapy. Patients were randomised 1:1 to double-blind ezetimibe/simvastatin 10/20 mg or rosuvastatin 10 mg for 6 weeks. Least squares mean percent change from baseline and 95% confidence intervals in lipid efficacy parameters were calculated for the population and within subgroups. Treatment with ezetimibe/simvastatin was significantly more effective than rosuvastatin at lowering low-density lipoprotein cholesterol, total cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B (all $p < 0.001$). No significant differences in treatment effects were seen between the presence and absence of MetS. In this post-hoc analysis of high-risk hypercholesterolaemic patients the lipid-reducing effects of ezetimibe/simvastatin or rosuvastatin were not altered

significantly by the presence of MetS.

Azar, M., E. Valentin, et al. (2011). "Comparison of the effects of combination atorvastatin (40 mg) + ezetimibe (10 mg) versus atorvastatin (40 mg) alone on secretory phospholipase A2 activity in patients with stable coronary artery disease or coronary artery disease equivalent." American Journal of Cardiology 107(11): 1571-1574.

Secretory phospholipase A2 (sPLA2) is an enzyme that plays an important role in the pathogenesis of atherosclerosis and of adverse cardiovascular events. It is currently the target of emerging therapeutic agents. Our study was designed to investigate the effect of aggressive lowering of low-density lipoprotein (LDL) cholesterol with ezetimibe and atorvastatin on sPLA2 activity. We randomized 100 patients with stable coronary artery disease (CAD) or CAD equivalent (diabetes, stroke, or peripheral vascular disease) to receive ezetimibe 10 mg/day in association with atorvastatin 40 mg/day (combination therapy group) versus atorvastatin 40 mg/day and placebo (monotherapy group). Patients on statin therapy before inclusion were allowed to enter the study as long as the potency of the statin was lower than atorvastatin 40 mg/day. Lipid profile, high-sensitivity C-reactive protein (hs-CRP), and sPLA activity were measured at baseline and after 8 weeks of therapy. The decrease in LDL cholesterol was more significant in the combination therapy group, but the decrease in hs-CRP was similar. sPLA2 activity significantly decreased in the ezetimibe/atorvastatin group from 29 U/ml (interquartile range 23 to 35) to 26 U/ml (23 to 29, $p = 0.001$) but remained similar in the placebo/atorvastatin group (23 U/ml, 19 to 32, vs 22 U/ml, 19 to 28, $p = \text{NS}$). In a multivariate stepwise linear regression model, change in sPLA2 correlated with change in hs-CRP ($p < 0.001$), baseline LDL cholesterol level ($p = 0.001$), body mass index ($p = 0.003$), diabetes mellitus ($p = 0.04$) and combination therapy with ezetimibe/atorvastatin ($p = 0.05$). In conclusion, this study demonstrates that coadministration of ezetimibe and atorvastatin decreases sPLA2 activity. Copyright 2011 Elsevier Inc. All rights reserved.

Backes, J. M., C. A. Gibson, et al. (2012). "The high-dose rosuvastatin once weekly study (the HD-ROWS)." Journal of Clinical Lipidology 6(4): 362-367.

BACKGROUND: Alternative dosing is often used clinically to address common barriers with statin therapy, such as intolerance and cost. Previous findings have demonstrated significant and clinically similar reductions in low-density lipoprotein (LDL) cholesterol to daily dosing, when comparing similar total weekly doses.

OBJECTIVE: To determine whether rosuvastatin 80 mg once weekly produced comparable lipid and high-sensitivity C-reactive protein (hsCRP) changes to atorvastatin 10 mg daily, when measured at key points after last dose.

METHODS: This was a randomized, double-blind, parallel group, 8-week pilot study. Eligible subjects, 18 to 65 years of age, had documented dyslipidemia with LDL cholesterol >100 mg/dL and triglycerides <200 mg/dL. Participants were randomized to receive either rosuvastatin 80 mg once weekly ($n = 10$) or atorvastatin 10 mg daily ($n = 10$), for 8 weeks. Lipid panels and hsCRP were measured at baseline and 1-4 and 5-8 days after the last dose.

RESULTS: Participants in each arm experienced significant and comparable reductions from baseline in total cholesterol, total cholesterol/high-density lipoprotein cholesterol ratio, non-high-density lipoprotein cholesterol, and overall LDL cholesterol (-29%). Changes in

high-density lipoprotein cholesterol, triglycerides, and hsCRP were nonsignificant and similar between groups. Each regimen was well tolerated, with no major adverse events reported.

CONCLUSION: Rosuvastatin 80 mg once weekly produced comparable lipid changes to atorvastatin 10 mg daily when measured at specific points after the last dose. Our findings support previous data demonstrating a significant reduction in LDL-C with once weekly statin dosing. Copyright 2012 National Lipid Association. Published by Elsevier Inc. All rights reserved.

Bahadir, M. A., A. Oguz, et al. (2009). "Effects of different statin treatments on small dense low-density lipoprotein in patients with metabolic syndrome." Journal of Atherosclerosis & Thrombosis **16**(5): 684-90.

AIM: To compare the effects of different low-density lipoprotein (LDL) cholesterol-lowering statin treatments on small dense LDL (sd-LDL) in hypercholesterolemic patients with metabolic syndrome (MetS). **METHODS:** Forty hypercholesterolemic MetS patients >30 years of age were randomized to rosuvastatin (n=17) or other statins (n=23) groups. In the other statins group, those taking atorvastatin (n=12) were also evaluated separately. Statin doses were 10 mg/day rosuvastatin, 20 mg/day atorvastatin, 40 mg/day simvastatin, and 40 mg/day pravastatin. Treatment duration was planned to be 8 weeks. Sd-LDL levels were assessed at baseline and at the completion of treatment. **RESULTS:** After treatment, sd-LDL levels were significantly reduced in all 3 groups (from 29.6+/-24.8 mg/dL to 8.9+/-8.5 mg/dL in the rosuvastatin group, p=0.001; from 26.2+/-15 mg/dL to 14.8+/-9.6 mg/dL in the atorvastatin group, p=0.02; and from 29.1+/-16.5 mg/dL to 14.7+/-11.2 mg/dL in the other statins group, p=0.0001). There was no significant difference in the mean percent changes among groups. **CONCLUSION:** Significant reduction in sd-LDL levels was observed after 8 weeks of statin treatment in hypercholesterolemic patients with MetS. This effect was similar for all statins and can be considered a class effect.

Bardini, G., C. B. Giorda, et al. (2010). "Ezetimibe + simvastatin versus doubling the dose of simvastatin in high cardiovascular risk diabetics: a multicenter, randomized trial (the LEAD study)." Cardiovascular Diabetology **9**: 20.

BACKGROUND: The primary goal of therapy in patients with hypercholesterolemia and coronary heart disease (CHD) is reducing low-density lipoprotein cholesterol (LDL-C). This was a multicenter, randomized, double-blind, double-dummy study in patients with type 2 diabetes mellitus (T2DM). **METHODS:** Adult patients with T2DM and CHD (N = 93) on a stable dose of simvastatin 20 mg with LDL-C \geq 2.6 mmol/L (100 mg/dL) and \leq 4.1 mmol/L (160 mg/dL) were randomized to ezetimibe 10 mg plus simvastatin 20 mg (EZ + simva 10/20 mg) or simvastatin 40 mg for 6 weeks. Percent change in LDL-C, high-density lipoprotein cholesterol, and triglycerides was assessed. **RESULTS:** EZ + simva 10/20 mg produced a significantly greater change from treated baseline compared with simvastatin 40 mg in LDL-C (-32.2% vs -20.8%; p < 0.01) and total cholesterol (-20.6% vs -13.2%; p < 0.01). A greater proportion of patients achieved LDL-C < 2.6 mmol/L with EZ + simva 10/20 mg than with simvastatin 40 mg, but this was not statistically significant (78.4% vs 60%; odds ratio = 2.81; p = 0.052). Changes in high-density lipoprotein cholesterol and triglycerides were similar between treatments. Both

treatments were generally well-tolerated. CONCLUSIONS: These results demonstrate that EZ + simva 10/20 mg may provide a superior alternative for LDL-C lowering vs doubling the dose of simvastatin to 40 mg in hyperlipidemic patients with T2DM and CHD. In addition, the combination therapy may provide an alternative treatment for patients who require further LDL-C reduction than they can achieve with simvastatin 20 mg alone.

Bays, H. E., M. Averna, et al. (2013). "Efficacy and safety of ezetimibe added to atorvastatin versus atorvastatin uptitration or switching to rosuvastatin in patients with primary hypercholesterolemia." *American Journal of Cardiology* **112**(12): 1885-1895.

Hypercholesterolemic patients (n = 1,547) at high atherosclerotic cardiovascular disease risk with low-density lipoprotein cholesterol (LDL-C) levels >100 and <160 mg/dl while treated with atorvastatin 10 mg/day entered a multicenter, randomized, double-blind, active-controlled, clinical trial using two 6-week study periods. Period I compared the efficacy/safety of (1) adding ezetimibe 10 mg (ezetimibe) to stable atorvastatin 10 mg, (2) doubling atorvastatin to 20 mg, or (3) switching to rosuvastatin 10 mg. Subjects in the latter 2 groups who persisted with elevated LDL-C levels (>100 and <160 mg/dl) after period I, entered period II; subjects on atorvastatin 20 mg had ezetimibe added to their atorvastatin 20 mg, or uptitrated their atorvastatin to 40 mg; subjects on rosuvastatin 10 mg switched to atorvastatin 20 mg plus ezetimibe or uptitrated their rosuvastatin to 20 mg. Some subjects on atorvastatin 10 mg plus ezetimibe continued the same treatment into period II. At the end of period I, ezetimibe plus atorvastatin 10 mg reduced LDL-C significantly more than atorvastatin 20 mg or rosuvastatin 10 mg (22.2% vs 9.5% or 13.0%, respectively, p <0.001). At the end of period II, ezetimibe plus atorvastatin 20 mg reduced LDL-C significantly more than atorvastatin 40 mg (17.4% vs 6.9%, p <0.001); switching from rosuvastatin 10 mg to ezetimibe plus atorvastatin 20 mg reduced LDL-C significantly more than uptitrating to rosuvastatin 20 mg (17.1% vs 7.5%, p <0.001). Relative to comparative treatments, ezetimibe added to atorvastatin 10 mg (period I) or atorvastatin 20 mg (period II) produced significantly greater percent attainment of LDL-C targets <100 or <70 mg/dl, and significantly greater percent reductions in total cholesterol, non-high-density lipoprotein cholesterol, most lipid and lipoprotein ratios, and apolipoprotein B (except ezetimibe plus atorvastatin 20 vs atorvastatin 40 mg). Reports of adverse experiences were generally similar among groups. In conclusion, treatment of hypercholesterolemic subjects at high cardiovascular risk with ezetimibe added to atorvastatin 10 or 20 mg produced significantly greater improvements in key lipid parameters and significantly greater attainment of LDL-C treatment targets than doubling atorvastatin or switching to (or doubling) rosuvastatin at the compared doses. Copyright 2013 Elsevier Inc. All rights reserved.

Bellia, A., S. Rizza, et al. (2010). "Early vascular and metabolic effects of rosuvastatin compared with simvastatin in patients with type 2 diabetes." *Atherosclerosis* **210**(1): 199-201.

OBJECTIVE: To compare the short-term effects of rosuvastatin and simvastatin on insulin-resistance and endothelial dysfunction in middle-aged patients with type 2 diabetes and mild untreated dyslipidemia. METHODS AND DESIGN: 29 Subjects randomly assigned to rosuvastatin 20mg/daily or simvastatin 20mg/daily for 4 weeks. Following data collected both pre- and post-treatment: fasting glucose, lipids, hs CRP,

TNF-alpha, insulin sensitivity measured with euglycemic-hyperinsulinemic clamp and flow-mediated dilation with brachial artery reactivity technique. RESULTS: Both treatments markedly reduced LDL cholesterol ($p < 0.001$ for both). Insulin sensitivity did not change from relative baseline values in both groups, as well as fasting glucose and adiponectin. Simvastatin significantly improved flow-mediated dilation ($p < 0.01$), to a greater extent than in patients taking rosuvastatin ($p = 0.09$). We found no association between flow-mediated dilation improvement, LDL reduction and changes in hs CRP levels. CONCLUSION: In type 2 diabetic individuals rosuvastatin was less effective than simvastatin at improving endothelium-dependent vasodilation within one month, without affecting insulin-resistance, adiponectin levels and inflammation. Copyright 2009 Elsevier Ireland Ltd. All rights reserved.

Boh, M., G. Opolski, et al. (2011). "Therapeutic equivalence of the generic and the reference atorvastatin in patients with increased coronary risk." International Angiology 30(4): 366-374.

AIM: Generic drugs are more and more frequently used instead of originators. However, uncertainty exists with respect to therapeutic equivalence of generic product with originator one. Therefore, in this study efficacy and safety of generic atorvastatin was compared to reference product. In patients with increased low density lipoprotein cholesterol (LDL-C) levels of cholesterol and changes of total coronary risk were followed.

METHODS: A randomized, double-blind, multicenter parallel study was carried out in 22 centers. The study included 148 subjects with LDL-C higher than 3 mmol/L and increased coronary risk ($> 9.5\%$ in 10 years calculated according to PROCAM algorithm). After a four-week placebo run-in period, patients were randomly assigned to receive the generic or the reference atorvastatin for 12 weeks. The initial dose of the drugs was 10 mg or 20 mg depending on the baseline LDL-C value. After six weeks the dose was increased to 20 mg or 40 mg in patients who had not reached the target LDL-C value of 2.99 mmol/L.

RESULTS: Altogether 117 patients have been analysed in the per-protocol analysis. The GA was proven to be equally effective to the reference product as shown by the significantly equal reduction in LDL-C (GA: 37.8%, RA: 38.4%, $P = NS$) using the non-inferiority statistical analysis. Also other lipid parameters were significantly lowered by both drugs with the exception of HDL-C. Both drugs significantly reduced absolute coronary risk by 13% and 13.3% for the generic and the reference atorvastatin, respectively. Systolic blood pressure was also significantly reduced by approximately 10 mmHg in both study groups. Both products had similar adverse events profile. No cases of therapy withdrawal due to safety were recorded.

CONCLUSION: Both the generic and the reference atorvastatin were equally effective in correcting the lipid profile and reducing calculated absolute coronary risk in patients with hyperlipidemia and increased coronary risk. Both treatments were equally well tolerated.

Brouwers, F. P., F. W. Asselbergs, et al. (2011). "Long-term effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria: Ten years of follow-up of Prevention of Renal and Vascular End-stage Disease Intervention Trial (PREVEND IT)." American Heart Journal 161(6): 1171-1178.

BACKGROUND: The PREVEND IT investigated whether treatment targeted at lowering urinary albumin excretion (UAE) would reduce adverse cardiovascular events. We obtained extended follow-up data to approximately 10 years to investigate the long-term effects of fosinopril 20 mg and pravastatin 40 mg on cardiovascular outcomes in subjects with UAE >15 mg per 24 hours.

METHODS: The original PREVEND IT consisted of 864 participants and 839 survivors after 4 years. For every survivor, the primary end point determined by the combined incidence of cardiovascular mortality and hospitalization for cardiovascular morbidity was registered in several national databases and electronic hospital systems.

RESULTS: Mean total follow-up of the extended PREVEND IT was 9.5 years (range 9.4-10.7 years). Four years of treatment with fosinopril was not associated with a reduction in the primary end point compared with placebo (hazard ratio 0.87, 95% CI 0.61-1.24 [P = .42]) during long-term follow-up. After 9.5 years, subjects with a baseline UAE in the upper quintile (>50 mg/24 hours) had a total event rate of 29.5% and were at a higher risk for developing cardiovascular disease compared with less UAE (hazard ratio 2.03, 95% CI 1.38-2.97 [P <= .01]). In addition, 4 years of fosinopril treatment resulted in a risk reduction of 45% (95% CI 6%-75% [P = .04]) in this group compared with placebo. Subjects originally assigned to pravastatin had no overall risk reduction in the primary end point (P = .99).

CONCLUSIONS: Elevated UAE is associated with increased cardiovascular mortality and morbidity after 9.5 years of follow-up, with a doubling of the risk if the UAE is >50 mg per 24 hours. In this group, the benefits of 4-year treatment with fosinopril were sustained during posttrial follow-up for cardiovascular mortality and morbidity. We propose that UAE be used to estimate risk in the general population and that large clinical trials be designed to confirm the hypothesis that angiotensin-converting enzyme-inhibitor treatment may be beneficial in patients with mildly elevated UAE despite the absence of other comorbidities. Copyright 2011 Mosby, Inc. All rights reserved.

Eriksson, M., D. Budinski, et al. (2011). "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.

Eriksson, M., D. Budinski, et al. (2011). "Long-term efficacy of pitavastatin versus simvastatin." Advances in Therapy 28(9): 799-810.

INTRODUCTION: Pitavastatin is a novel, potent, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor. This study compared the long-term efficacy of pitavastatin and simvastatin in dyslipidemic patients at high risk of coronary heart disease.

METHODS: A 44-week blinded extension study was conducted at 24 centers in five European countries for patients who had previously completed a 12-week randomized, double-blind core study in which they received pitavastatin 4 mg or simvastatin 40 mg once daily. Patients originally randomized to pitavastatin 4 mg continued at the same dose throughout the extension study ($n = 121$). In simvastatin-treated patients ($n = 57$), the dose was increased to 80 mg in five patients who had not attained the National Cholesterol Education Program (NCEP) target for low-density lipoprotein cholesterol (LDL-C) during the core study. Primary endpoints were the proportion of patients attaining the NCEP and European Atherosclerosis Society (EAS) LDL-C targets, and the NCEP target for non-high-density lipoprotein cholesterol (non-HDL-C) at weeks 16 and 44.

RESULTS: Of the 178 patients who entered the extension study, 156 patients (109 in the pitavastatin group, 47 in the simvastatin groups) completed the 44-week treatment period. At week 44, NCEP and EAS targets were attained by 81.7% and 84.2%, respectively, of pitavastatin-treated patients, and 75.4% and 73.7%, respectively, of simvastatin-treated patients. NCEP targets for non-HDL-C were achieved by 79.2% of pitavastatin-treated patients and 70.2% of simvastatin-treated patients. Both treatments were generally well tolerated, but pitavastatin 4 mg was associated with a numerically lower incidence of discontinuations due to treatment-emergent adverse events (5.8% vs. 10.5% of patients) and a lower rate of myalgia (4.1% vs. 12.3%) compared with simvastatin 40-80 mg.

CONCLUSION: Pitavastatin 4 mg provides long-term efficacy similar to that of simvastatin 40-80 mg. Further studies should ascertain whether trends suggesting that pitavastatin may exhibit a more favorable long-term tolerability profile are statistically significant.

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. Copyright Copyright 2010 Elsevier Inc. All rights reserved.

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-hydroxy-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; $\times 1.25 \geq$ and $\leq \times 2.5$ 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 $>3 \times$ 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.

Her, A. Y., J. Y. Kim, et al. (2010). "Effects of atorvastatin 20 mg, rosuvastatin 10 mg, and atorvastatin/ezetimibe 5 mg/5 mg on lipoproteins and glucose metabolism." Journal of Cardiovascular Pharmacology & Therapeutics 15(2): 167-74.

The aim of this study was to compare the effects of 3 different statin regimens that have equivalent low-density lipoprotein cholesterol (LDL-C) lowering efficacy on the apolipoprotein B/A1 ratio and glucose metabolism. After a 4-week dietary lead-in, 90 hypercholesterolemic patients were randomly assigned to 1 of 3 treatment groups for 8 weeks: atorvastatin 20 mg, rosuvastatin 10 mg, or atorvastatin/ezetimibe 5 mg/5 mg. At

drug treatment week 8, we compared the percentage changes in lipid parameters, apolipoprotein B/A1 ratio, hemoglobin A1c, and homeostasis model assessment-insulin resistance (HOMA-IR) from baseline. Seventy-six patients completed the study and the percentage changes in LDL-C were comparable among the groups. However, the percentage reduction in the apolipoprotein B/A1 ratio was significantly greater in the rosuvastatin group (-47% +/- 14%, P = .04) and the combination group (-46% +/- 8%, P = .05) than in the atorvastatin group (-39% +/- 11%). The percentage increase in hemoglobin A1c was small but significantly greater in the atorvastatin group compared to the combination group (3.0% +/- 5.2% and -0.4% +/- 4.0%, P = .03). The effect of rosuvastatin on hemoglobin A1c was not different from those of the other 2 regimens. The effects of 3 statin regimens were similar on HOMA-IR. In conclusion, 3 statin regimens have differential effect on apolipoprotein B/A1 and glycemic control after comparable LDL-C reduction.

Hing Ling, P. K., F. Civeira, et al. (2012). "Ezetimibe/simvastatin 10/40 mg versus atorvastatin 40 mg in high cardiovascular risk patients with primary hypercholesterolemia: a randomized, double-blind, active-controlled, multicenter study." Lipids in Health & Disease 11: 18.

BACKGROUND: A considerable number of patients with severely elevated LDL-C do not achieve recommended treatment targets, despite treatment with statins. Adults at high cardiovascular risk with hypercholesterolemia and LDL-C ≥ 2.59 and ≤ 4.14 mmol/L (N = 250), pretreated with atorvastatin 20 mg were randomized to ezetimibe/simvastatin 10/40 mg or atorvastatin 40 mg for 6 weeks. The percent change in LDL-C and other lipids was assessed using a constrained longitudinal data analysis method with terms for treatment, time, time-by-treatment interaction, stratum, and time-by-stratum interaction. Percentage of subjects achieving LDL-C < 1.81 mmol/L, < 2.00 mmol/L, or < 2.59 mmol/L was assessed using a logistic regression model with terms for treatment and stratum. Tolerability was assessed.

RESULTS: Switching to ezetimibe/simvastatin resulted in significantly greater changes in LDL-C (-26.81% vs.-11.81%), total cholesterol (-15.97% vs.-7.73%), non-HDL-C (-22.50% vs.-10.88%), Apo B (-17.23% vs.-9.53%), and Apo A-I (2.56% vs.-2.69%) vs. doubling the atorvastatin dose (all p ≤ 0.002), but not HDL-C, triglycerides, or hs-CRP. Significantly more subjects achieved LDL-C < 1.81 mmol/L (29% vs. 5%), < 2.00 mmol/L (38% vs. 9%) or < 2.59 mmol/L (69% vs. 41%) after switching to ezetimibe/simvastatin vs. doubling the atorvastatin dose (all p < 0.001). The overall safety profile appeared generally comparable between treatment groups.

CONCLUSIONS: In high cardiovascular risk subjects with hypercholesterolemia already treated with atorvastatin 20 mg but not at LDL-C < 2.59 mmol/L, switching to combination ezetimibe/simvastatin 10/40 mg provided significantly greater LDL-C lowering and greater achievement of LDL-C targets compared with doubling the atorvastatin dose to 40 mg. Both treatments were generally well-tolerated.

TRIAL REGISTRATION: Registered at clinicaltrials.gov: NCT00782184.

Hongo, M., S. Kumazaki, et al. (2011). "Low-dose rosuvastatin improves arterial stiffness in high-risk Japanese patients with dyslipidemia 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.

Jimenez, J. G., J. B. Rosen, et al. (2013). "The efficacy and safety of ezetimibe/simvastatin combination compared with intensified lipid-lowering treatment strategies in diabetic subjects with and without metabolic syndrome." *Diabetes, Obesity & Metabolism* **15**(6): 513-522.

AIMS: The objective was to assess the consistency of effect of switching to ezetimibe/simvastatin 10/20mg versus doubling the baseline statin dose (to simvastatin 40mg or atorvastatin 20mg) or switching to rosuvastatin 10mg across subgroups of subjects with (n=617) and without (n=191) metabolic syndrome (MetS).

METHODS: This was a post hoc analysis of a randomized, double-blind, 6-week study of adults 18-79 years with cardiovascular disease and diabetes mellitus with low-density lipoprotein cholesterol (LDL-C) >70 and <160mg/dl. The percent change in LDL-C and other lipids was estimated within each subgroup separately. Safety and tolerability were assessed.

RESULTS: In subjects with MetS, percent changes in LDL-C and other lipids were greater with ezetimibe/simvastatin versus doubling baseline statin or numerically greater versus switching to rosuvastatin, except high-density lipoprotein cholesterol and apolipoprotein (Apo) AI (mean percent changes in LDL-C were: -22.49% ezetimibe/simvastatin, -9.64% doubled baseline statin and -19.20% rosuvastatin). In subjects without MetS, percent changes in LDL-C, total cholesterol and Apo B were greater with ezetimibe/simvastatin versus doubling baseline statin or numerically greater versus switching to rosuvastatin (mean percent changes in LDL-C were: -25.14% ezetimibe/simvastatin, -4.75% doubled baseline statin and -19.75% rosuvastatin). Safety profiles were generally similar.

CONCLUSION: These results showed that switching to ezetimibe/simvastatin 10/20mg was more effective at reducing LDL-C, total cholesterol and Apo B versus doubling the baseline statin dose to simvastatin 40mg or atorvastatin 20mg or switching to rosuvastatin 10mg regardless of MetS status. These results were generally similar to those of the full cohort. 2012 Blackwell Publishing Ltd.

Kim, S.-H., M.-K. Seo, et al. (2013). "Assessment of the efficacy and tolerability of 2 formulations of atorvastatin in Korean adults with hypercholesterolemia: a multicenter, prospective, open-label, randomized trial." Clinical Therapeutics 35(1): 77-86.

BACKGROUND: A manufacturer of atorvastatin is seeking marketing approval in Korea of a generic product for adult patients with primary hypercholesterolemia.

OBJECTIVE: The objective of this study was to compare the efficacy and tolerability of a new generic formulation of atorvastatin (test) with those of an original formulation of atorvastatin (reference) to satisfy regulatory requirements for marketing of the generic product in Korea.

METHODS: Patients enrolled were aged 20 to 79 years with documented primary hypercholesterolemia who did not respond adequately to therapeutic lifestyle changes and with a LDL-C level >100 mg/dL from a high-risk group of coronary artery disease patients. Eligible patients were randomized to receive 1 of the 2 formulations of atorvastatin 20 mg per day for 8 weeks. The primary end point was the percent change in LDL-C level from baseline to week 8. Secondary end points included the percent change in total cholesterol, triglycerides, HDL-C level, apolipoprotein B:apolipoprotein A-I ratio, LDL:HDL ratio, LDL-C particle size, high-sensitivity C-reactive protein from baseline to week 8, and achievement rate of the LDL-C goal.

RESULTS: A total of 298 patients (141 men and 157 women; 149 patients in each group; mean [SD] age, 62.4 [9.2] in the test group vs 60.3 [8.9] years in the reference group) were included. LDL-C levels were significantly decreased from baseline to week 8 in both groups, and there was no significant difference in the percent change in LDL-C level between groups (-44.0% [17.2%] in the test group, -45.4% [16.9%] in the reference group; $P = 0.49$). The between-group differences in the percent changes in total cholesterol and triglyceride levels were not statistically significant. In addition, there was no significant difference between the 2 groups in percent changes in HDL-C, apolipoprotein B:apolipoprotein A-I ratio, LDL-C:HDL-C ratio, LDL-C particle size, high-sensitivity C-reactive protein, and the achievement rate of the LDL-C goal. Two (1.3%) patients in the reference group ($N = 150$) experienced treatment-related serious adverse events (AEs): toxic hepatitis and aggravation of chest pain. Common AEs were cough (4.1%), myalgia (2.1%), and indigestion (1.4%) in the test formulation group and cough (5.3%), creatine kinase elevation (2.7%), and edema (0.7%) in the reference formulation group; however, the differences in overall prevalence of AEs between the 2 treatment groups was not significant ($P = 0.88$).

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. Copyright 2010 European Federation of Internal Medicine. Published by Elsevier B.V. All rights reserved.

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, S.-H., S.-M. Kang, et al. (2011). "The effects of statin monotherapy and low-dose statin/ezetimibe on lipoprotein-associated phospholipase A2." *Clinical Cardiology* 34(2): 108-112.

BACKGROUND: Many of the pleiotropic effects of statins remain to be elucidated. **HYPOTHESIS:** Different statin regimens with similar lipid-lowering efficacy may have different effects on biomarkers of atherothrombosis including lipoprotein-associated phospholipase A2 (Lp-PLA2). **METHODS:** After a 4-week dietary lead-in, 82 hypercholesterolemic patients were randomized to 1 of 2 treatment groups: atorvastatin 20 mg or atorvastatin/ezetimibe 5 mg/5 mg. After 8 weeks of drug treatment, the groups were compared for percent change in lipid parameters, Lp-PLA2 , interleukin-6 (IL-6), monocyte chemoattractant protein-1, and fibrinogen. **RESULTS:** Low-density lipoprotein cholesterol (LDL-C) lowering was comparable between the 2 groups (-47% +/- 11% and -49% +/- 7% in the atorvastatin and combination groups, respectively). Although Lp-PLA2 was reduced in both groups, the reduction was greater in the atorvastatin group (-42% and -9% [median], respectively, $P = 0.03$). Although IL-6 was decreased only in the atorvastatin group, IL-6 changes were not significantly different between the 2 groups. The changes in monocyte chemoattractant protein-1 and fibrinogen were similar in each group. **CONCLUSIONS:** Atorvastatin monotherapy was stronger at reducing plasma Lp-PLA2 than the low-dose atorvastatin/ezetimibe combination after equivalent LDL-C lowering. This result may provide evidence of potential statin effects beyond the lowering of LDL-C. 2011 Wiley Periodicals, Inc.

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 $(\text{TAV at 6 months} - \text{TAV at baseline}) / (\text{TAV at baseline}) \times 100$. 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 ($-3.9 \pm 11.9\%$ vs $-7.4 \pm 10.6\%$, 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 segment 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, S.-H., S. Park, et al. (2012). "Effect of atorvastatin monotherapy and low-dose atorvastatin/ezetimibe combination on fasting and postprandial triglycerides in combined hyperlipidemia." Journal of Cardiovascular Pharmacology & Therapeutics 17(1): 65-71.

Postprandial triglyceride (TG) levels are easy to measure and are associated with future cardiovascular risk. The aim of this study was to compare the effects of statin monotherapy and low-dose statin/ezetimibe on lipid parameters including fasting and postprandial TG. After a 4-week dietary run-in period, 78 patients with combined hyperlipidemia were randomized into 1 of 2 treatment groups for 8 weeks: atorvastatin 20 mg or atorvastatin/ezetimibe 5 mg/5 mg. An oral fat load test was performed before and after the drug-treatment period. The low-dose combination had a tendency to decrease fasting TG more than atorvastatin monotherapy. The combination regimen showed a greater reduction in postprandial TG ($-13\% \pm 42\%$ and $-34\% \pm 30\%$, in the atorvastatin and combination groups, respectively, $P = .03$) and total cholesterol (TC; $P = .03$). The changes in low-density lipoprotein-cholesterol (LDL-C) and high-density lipoprotein-cholesterol (HDL-C) were not different between the 2 groups. The reduction in apo B/A1 was greater in the combination group ($-32\% \pm 19\%$ and $-42\% \pm 13\%$, in the atorvastatin and combination groups, respectively, $P = .02$). In conclusion, these results demonstrated a potential beneficial effect of low-dose atorvastatin/ezetimibe combination treatment on postprandial TG control after comparable LDL-C lowering in patients with combined hyperlipidemia.

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 $-38.6 \pm 18.0\%$ vs. atorvastatin $-34.4 \pm 15.5\%$; $p = 0.059$). 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 ($2.8 \pm 10.0\%$ vs. $-1.8 \pm 9.8\%$; $p = 0.002$). In the per-protocol analysis, improvement in ApoB/ApoA1 was significantly greater in the ezetimibe/simvastatin group ($-42.8 \pm 11.8\%$ vs. $-36.7 \pm 13.2\%$; $p = 0.019$). 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, B., H. M. Cao, et al. (2011). "Effects of rosuvastatin versus atorvastatin on rho-associated coiled-coil containing protein kinase activity and endothelial function in patients with atherosclerosis." Journal of International Medical Research **39**(6): 2314-2322.

This randomized, double-blind, parallel-design study compared the short-term effects of rosuvastatin and atorvastatin on serum lipids and markers of inflammation and endothelial function in patients with stable atherosclerosis. Patients received either 10 mg/day rosuvastatin ($n = 18$) or 20 mg/day atorvastatin ($n = 18$), orally, for 4 weeks. Serum lipids, high-sensitivity C-reactive protein (hsCRP), Rho-associated coiled-coil containing protein kinase (ROCK) activity and flow-mediated dilation (FMD) of the brachial artery were assessed before and after therapy. Both statins produced significant reductions in total cholesterol, low-density lipoprotein cholesterol (LDL-C), triglyceride and hsCRP levels, and significant increases in FMD. Both statins significantly reduced

ROCK activity and inhibition was significantly greater with rosuvastatin. There was no correlation between ROCK activity and LDL-C level in either group. There was a significant correlation between ROCK activity and FMD for both statins, but no correlations between FMD and LDL-C or hsCRP levels. Short-term treatment with either rosuvastatin or atorvastatin inhibits ROCK activity independent of cholesterol reduction, and improves endothelium dysfunction in patients with atherosclerosis.

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 \geq 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.

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 aminothiols 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 mm³ (95% CI, -7.52 to -5.12), as compared with -4.42 mm³ (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.).

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 ≥ 1.1 mm 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.

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.

Padhy, B. M., R. Yadav, et al. (2013). "Hypolipidaemic and anti-inflammatory effects of fixed dose combination of atorvastatin plus ezetimibe in Indian patients with dyslipidaemia." Singapore Medical Journal **54**(2): 90-95.

INTRODUCTION: We aimed to assess the efficacy of fixed dose combination of atorvastatin plus ezetimibe in Indian patients with dyslipidaemia.

METHODS: A double-blind study was conducted to assess the effect of fixed dose combination of ezetimibe 10 mg plus atorvastatin 10 mg on lipid profile, oxidised low-density lipoprotein (ox-LDL), high-sensitivity C-reactive protein (hsCRP) and soluble intercellular cell adhesion molecule (sICAM) in dyslipidaemic patients with or at high risk of coronary artery disease, and compare it with atorvastatin 10 mg monotherapy. 30 patients were randomised to receive ezetimibe plus atorvastatin or atorvastatin once daily for four weeks.

RESULTS: Of the 30 patients, 10 men and 5 women (mean age 54.3 + 1.6 years) received ezetimibe plus atorvastatin, while 13 men and 2 women (mean age 53.7 + 2.8 years) received only atorvastatin. The combination treatment significantly reduced total cholesterol (percentage treatment difference -14.4 + 6.5, 95% confidence interval [CI] -1.0 to -27.7; $p = 0.041$) and LDL cholesterol (LDL-C; percentage treatment difference -19.9 + 6.1, 95% CI -7.4 to -32.4; $p = 0.003$) compared to atorvastatin monotherapy. 13 patients on combination treatment achieved the National Cholesterol Education Program target for LDL-C as compared to 9 patients on atorvastatin monotherapy ($p = 0.032$). Significant reductions in very low-density lipoprotein cholesterol, triglyceride, ox-LDL and sICAM were observed with combination treatment compared to atorvastatin monotherapy. However, no significant change was seen in high-density lipoprotein cholesterol or hsCRP levels between the two groups.

CONCLUSION: Combination treatment with atorvastatin and ezetimibe had relatively better lipid-lowering and anti-inflammatory efficacy than atorvastatin monotherapy.

Park, J. S., Y. J. Kim, et al. (2010). "Comparative study of low doses of rosuvastatin and atorvastatin on lipid and glycemic control in patients with metabolic syndrome and hypercholesterolemia." *Korean Journal of Internal Medicine* **25**(1): 27-35.

BACKGROUND/AIMS: This multicenter, open-labeled, randomized trial was performed to compare the effects of rosuvastatin 10 mg and atorvastatin 10 mg on lipid and glycemic control in Korean patients with nondiabetic metabolic syndrome. **METHODS:** In total, 351 patients who met the modified National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria for metabolic syndrome with low-density lipoprotein cholesterol (LDL-C) levels ≥ 130 mg/dL were randomized to receive either rosuvastatin 10 mg ($n = 173$) or atorvastatin 10 mg ($n = 178$) for over 6 weeks. **RESULTS:** After 6 weeks of treatment, greater reductions in total cholesterol (-35.94 +/- 11.38 vs. -30.07 +/- 10.46%, $p < 0.001$), LDL-C (48.04 +/- 14.45 vs. 39.52 +/- 14.42%, $p < 0.001$), non-high-density lipoprotein cholesterol (-42.93 +/- 13.15 vs. -35.52 +/- 11.76%, $p < 0.001$), and apolipoprotein-B (-38.7 +/- 18.85 vs. -32.57 +/- 17.56%, $p = 0.002$) levels were observed in the rosuvastatin group as compared to the atorvastatin group. Overall, the percentage of patients attaining the NCEP ATP III goal was higher with rosuvastatin as compared to atorvastatin (87.64 vs. 69.88%, $p < 0.001$). Changes in glucose and insulin levels, and homeostasis model assessment of insulin resistance index were not significantly different between the two groups. The safety and tolerability of the two agents were similar. **CONCLUSIONS:** Rosuvastatin 10 mg was more effective than atorvastatin 10 mg in achieving NCEP ATP III LDL-C goals in

patients with nondiabetic metabolic syndrome, especially in those with lower NCEP ATP III target level goals.

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.

Pesaro, A. E. P., C. V. Serrano, Jr., et al. (2012). "Pleiotropic effects of ezetimibe/simvastatin vs. high dose simvastatin." *International Journal of Cardiology* 158(3): 400-404.

BACKGROUND: In the setting of stable coronary artery disease (CAD), it is not known if the pleiotropic effects of cholesterol reduction differ between combined ezetimibe/simvastatin and high-dose simvastatin alone.

OBJECTIVE: We sought to compare the anti-inflammatory and antiplatelet effects of ezetimibe 10mg/simvastatin 20mg (E10/S20) with simvastatin 80 mg (S80).

METHODS AND RESULTS: CAD patients (n=83, 63 +/- 9 years, 57% men) receiving S20, were randomly allocated to receive E10/S20 or S80, for 6 weeks. Lipids, inflammatory markers (C-reactive protein, interleukin-6, monocyte chemoattractant protein-1, soluble CD40 ligand and oxidized LDL), and platelet aggregation (platelet function analyzer [PFA]-100) changes were determined. Baseline lipids, inflammatory markers and PFA-100 were similar between groups. After treatment, E10/S20 and S80 patients presented, respectively: (1) similar reduction in LDL-C (29 +/- 13% vs. 28 +/- 30%, p=0.46), apo-B (18 +/- 17% vs. 22 +/- 15%, p=0.22) and oxidized LDL (15 +/- 33% vs. 18 +/- 47%, p=0.30); (2) no changes in inflammatory markers; and, (3) a higher increase of the PFA-100 with E10/S20 than with S80 (27 +/- 43% vs. 8 +/- 33%, p=0.02).

CONCLUSIONS: These data suggest that among stable CAD patients treated with S20, (1) both E10/S20 and S80 were equally effective in further reducing LDL-C; (2) neither treatment

had any further significant anti-inflammatory effects; and (3) E10/S20 was more effective than S80 in inhibiting platelet aggregation. Thus, despite similar lipid lowering and doses 4x less of simvastatin, E10/S20 induced a greater platelet inhibitory effect than S80. Copyright 2011 Elsevier Ireland Ltd. 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.

Polis, A. B., N. Abate, et al. (2009). "Low-density lipoprotein cholesterol reduction and goal achievement with ezetimibe/simvastatin versus atorvastatin or rosuvastatin in patients with diabetes, metabolic syndrome, or neither disease, stratified by National Cholesterol Education Program risk category." Metabolic Syndrome & Related Disorders 7(6): 601-10.

BACKGROUND: Patients with diabetes mellitus (DM) and metabolic syndrome are at increased risk of coronary heart disease (CHD). Studies have shown differential statin efficacy on low-density lipoprotein cholesterol (LDL-C) by CHD risk strata. **OBJECTIVE:** The aim of this study was to evaluate the consistency of effect with ezetimibe/simvastatin (E/S) combination therapy, atorvastatin, or rosuvastatin in patients with DM, metabolic syndrome, or neither condition (No DM/metabolic syndrome), stratified by the National Cholesterol Education Panel Adult Treatment Panel III (NCEP ATP III) CHD risk group. **METHODS:** Post hoc analyses of 2 multicenter, double-blind, randomized, 6-week studies comparing E/S 10/10, 10/20, 10/40, or 10/80 mg with either atorvastatin 10, 20, 40, or 80 mg, or rosuvastatin 10, 20, or 40 mg. Treatments were compared by pooling

across all doses for LDL-C reduction and NCEP LDL-C goal attainment in patients with DM, metabolic syndrome without DM, or No DM/metabolic syndrome across NCEP CHD risk strata. **RESULTS:** NCEP LDL-C goal attainment was lowest in the high-risk group with atherosclerotic vascular disease (12-64%) and greatest in the moderate and low-risk groups (84-100%). In contrast, LDL-C reduction was generally similar irrespective of disease or risk subgroup. All treatments were generally well tolerated, with overall similar safety regardless of disease and risk level. **CONCLUSIONS:** In these studies, CHD risk strata were inversely related to the likelihood of attaining NCEP LDL-C goals, but did not appear to affect the percentage LDL-C change from baseline. This demonstrates the need for especially aggressive cholesterol lowering necessary to reach the lower LDL-C goal for high-risk patients.

Puccetti, L., F. Santilli, et al. (2011). "Effects of atorvastatin and rosuvastatin on thromboxane-dependent platelet activation and oxidative stress in hypercholesterolemia." *Atherosclerosis* 214(1): 122-128.

OBJECTIVES: We examined the time-dependent effects of atorvastatin and rosuvastatin on in vivo oxidative stress and platelet activation, to assess whether these phenomena are related to any pleiotropic effect of any statin or to their LDL-lowering effect. We also asked whether the presence of specific allele frequencies in carriers of the 3'UTR/lectin-like oxidized LDL receptor-1 (LOX-1) polymorphism may influence the effect of either statin.

METHODS: We included 60 hypercholesterolemic subjects, previously screened for LOX-1 3'UTR polymorphism, randomized, according to genetic profile (15 T and 15 C carriers for each arm), to atorvastatin 20mg/day or rosuvastatin 10mg/day.

RESULTS: After 8 weeks, atorvastatin and rosuvastatin were associated with comparable, significant reductions in LDL cholesterol (40.8% and 43.6%, respectively), plasma hs-CRP (9.5% vs. 13.8%), urinary 11-dehydro-thromboxane (TX) B(2) (38.9% vs. 27.1%) and 8-iso-prostaglandin (PG) F(2) (39.4% vs. 19.4%). The impact of rosuvastatin or atorvastatin on CRP, 8-iso-PGF(2), and 11-dehydro-TXB(2) did not differ according to the LOX-1 haplotype. On multiple regression analyses, only CRP and LDL were independent predictors of 11-dehydro-TXB(2), and only LDL was a significant predictor of 8-iso-PGF(2).

CONCLUSIONS: Both atorvastatin and rosuvastatin cause comparable reductions of thromboxane-dependent platelet activation, lipid peroxidation and inflammation. The presence of 3'UTR/LOX-1 polymorphism does not affect the changes induced by either statin. Copyright A 2010 Elsevier Ireland Ltd. 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.

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 ($n = 30$), simvastatin 40 mg plus ezetimibe 10 mg plus 25 g of fiber ($n = 28$), or simvastatin 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.

Robinson, J. G., C. M. Ballantyne, et al. (2011). "Achievement of specified low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol apolipoprotein B, and high-sensitivity C-reactive protein levels with ezetimibe/simvastatin or atorvastatin in metabolic syndrome patients with and without atherosclerotic vascular disease (from the VYMET study)." *Journal of Clinical Lipidology* 5(6): 474-482.

BACKGROUND: Metabolic syndrome (MetS) and atherosclerotic vascular disease

(AVD) are associated with increased coronary heart disease risk.

OBJECTIVE: To assess percent change from baseline in lipids and high-sensitivity C-reactive protein (hs-CRP) levels and the proportion of subjects reaching specified low-density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol (HDL-C) and apolipoprotein B (Apo B) single, dual, and triple targets and hs-CRP <2 mg/L among subjects with and without AVD treated with ezetimibe/simvastatin or atorvastatin for 6 weeks.

METHODS: Adults (N= 1143) with MetS and hypercholesterolemia were randomized to starting and next higher doses of ezetimibe/simvastatin (10/20 or 10/40 mg) or atorvastatin (10, 20, or 40 mg).

RESULTS: Ezetimibe/simvastatin produced significantly greater reductions in evaluated lipids than atorvastatin for most prespecified dose comparisons. More subjects without AVD achieved LDL-C levels <100 mg/dL, non-HDL-C levels <130 mg/dL, and dual LDL-C/non-HDL targets (83%-92% vs 62%-76%) and ApoB <90 mg/dL or triple targets (65%-75% vs 41%-49%) with 40 mg of atorvastatin or 10/20-40 mg of ezetimibe/simvastatin compared with 10 or 20 mg of atorvastatin, respectively. More subjects with AVD achieved LDL-C <70 mg/dL and non-HDL-C <100 mg/dL single and dual targets (65%-80%) and Apo B <80 mg/dL (53%-63%) with 10/20-40 mg of ezetimibe/simvastatin than with 40 mg of atorvastatin (40%-49%). More subjects achieved triple lipid targets with 10/20-40mg of ezetimibe/simvastatin versus 10-40 mg of atorvastatin (50%-63% vs 24%-40%). Achievement of hs-CRP <2 mg/L was similar across all doses regardless of AVD status.

CONCLUSIONS: More intensive therapy was required for >80% of subjects to achieve LDL-C <100 mg/dL and non-HDL-C <130 mg/dL and for the majority of subjects to achieve lower levels of LDL-C <70 mg/dL, non-HDL-C <100 mg/dL, and/or Apo B <90 mg/dL. The effect of ezetimibe on cardiovascular risk reduction has yet to be established. (Clintrials.gov no: NCT00409773). Copyright 2011 National Lipid Association. Published by Elsevier Inc. All rights reserved

Robinson, J. G., C. M. Ballantyne, et al. (2013). "Age, abdominal obesity, and baseline high-sensitivity C-reactive protein are associated with low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B responses to ezetimibe/simvastatin and atorvastatin in patients with metabolic syndrome." *Journal of Clinical Lipidology* 7(4): 292-303.

BACKGROUND: Treatment response to lipid-lowering therapy can vary in patients with the metabolic syndrome (MetS) due to various patient demographic and baseline characteristics.

OBJECTIVE: This study assessed the relationships between baseline characteristics and changes in lipid variables, high-sensitivity C-reactive protein (hs-CRP) and attainment of prespecified low-density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein cholesterol (non-HDL-C) levels in MetS patients treated with ezetimibe/simvastatin and atorvastatin.

METHODS: This is a post-hoc analysis of a multicenter, double-blind, randomized, 6-week parallel study in >1000 hypercholesterolemic subjects (median age of 59 years) with MetS and moderately high/high coronary heart disease risk who were treated with ezetimibe/simvastatin (10/20 and 10/40 mg) or atorvastatin (10, 20, 40 mg). Factors that could affect these treatments were assessed by multivariate analysis.

RESULTS: Increasing age, abdominal obesity (waist circumference > 40/35 inches for men/women), and lower baseline hs-CRP were significant predictors of greater reductions in LDL-C, non-HDL-C, apolipoprotein B, total cholesterol, triglycerides, and very-low-density lipoprotein cholesterol but not for changes in HDL-C or apolipoprotein AI; effects of race and baseline triglycerides, non-HDL-C, LDL-C, or HDL-C levels were more limited. Age > 65 years (versus <65 years) was also associated with significantly greater attainment of all LDL-C and non-HDL-C targets, whereas abdominal obesity, gender (female > male) and lower baseline LDL-C, non-HDL-C, triglycerides, and hs-CRP were associated with improved attainment for some of these targets. Blood pressure, fasting glucose, Homeostasis Model Assessment of Insulin Resistance tertiles, and diabetes did not predict response for any efficacy variable. Ezetimibe/simvastatin treatment (versus atorvastatin) was a significant predictor for change in most efficacy variables.

CONCLUSIONS: Treatment responses to ezetimibe/simvastatin and atorvastatin in at-risk patients with the MetS were related to age (> 65 years), abdominal obesity, and lower baseline hs-CRP. Ezetimibe/simvastatin treatment was found to be consistently more effective than atorvastatin at the specified dose comparisons across these subgroups. The clinical value of predictive factors requires further study in outcome trials. Copyright 2013 National Lipid Association. Published by Elsevier Inc. All rights reserved.

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.

Rotella, C. M., A. Zaninelli, et al. (2010). "Ezetimibe/simvastatin vs simvastatin in coronary heart disease patients with or without diabetes." Lipids in Health & Disease **9**: 80.

BACKGROUND: Treatment guidelines recommend LDL-C as the primary target of therapy in patients with hypercholesterolemia. Moreover, combination therapies with lipid-lowering drugs that have different mechanisms of action are recommended when it is not possible to attain LDL-C targets with statin monotherapy. Understanding which treatment or patient-related factors are associated with attaining a target may be clinically

relevant. **METHODS:** Data were pooled from two multicenter, randomized, double-blind studies. After stabilization on simvastatin 20 mg, patients with coronary heart disease (CHD) alone and/or type 2 diabetes mellitus (T2DM) were randomized to ezetimibe 10 mg/simvastatin 20 mg (EZ/Simva) or simvastatin 40 mg. The change from baseline in low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), TC/HDL-C ratio, triglycerides, and the proportion of patients achieving LDL-C < 2.6 mmol/L (100 mg/dL) after 6 weeks of treatment were assessed, and factors significantly correlated with the probability of achieving LDL-C < 2.6 mmol/L in a population of high cardiovascular risk Italian patients were identified. A stepwise logistic regression model was conducted with LDL-C < 2.6 mmol/L at endpoint as the dependent variable and study, treatment, gender, age (> or = 65 years or < 65 years), as independent variables and baseline LDL-C (both as continuous and discrete variable). **RESULTS:** EZ/Simva treatment (N = 93) resulted in significantly greater reductions in LDL-C, TC, and TC/HDL-C ratio and higher attainment of LDL-C < 2.6 mmol/L vs doubling the simvastatin dose to 40 mg (N = 106). Study [including diabetic patients (OR = 2.9, p = 0.003)], EZ/Simva treatment (OR = 6.1, p < 0.001), and lower baseline LDL-C (OR = 0.9, p = 0.001) were significant positive predictors of LDL-C target achievement. When baseline LDL-C was expressed as a discrete variable, the odds of achieving LDL-C < 2.6 mmol/L was 4.8 in favor of EZ/Simva compared with Simva 40 mg (p < 0.001), regardless of baseline LDL-C level. **CONCLUSION:** EZ/Simva is an effective therapeutic option for patients who have not achieved recommended LDL-C treatment targets with simvastatin 20 mg monotherapy. **TRIAL REGISTRATION:** Clinical trial registration numbers: NCT00423488 and NCT00423579.

Rudofsky, G., P. Reismann, et al. (2012). "Identical LDL-cholesterol lowering but non-identical effects on NF-kB activity: High dose simvastatin vs combination therapy with ezetimibe." *Atherosclerosis* 223(1): 190-196.

OBJECTIVE: Lowering LDL-cholesterol by statins has been proven to be associated with reduction of proinflammatory regulators e.g. activation of the transcription factor NF-kB. To our knowledge, anti-inflammatory potential of newer cholesterol lowering agents such as ezetimibe is less intensively studied. Therefore we analyzed the effects of equipotent LDL-lowering therapy with simvastatin alone compared to a combination with ezetimibe on NF-kB activation in peripheral blood mononuclear cells (PBMCs) of patients with type 2 diabetes.

METHODS: Thirty-one patients with type 2 diabetes were included in a double-blind, randomized trial receiving either 80 mg simvastatin (sim80; n = 10) or a combination of 10 mg simvastatin and 10 mg ezetimibe (sim10eze10; n = 11) or placebo (n = 9) for eight weeks. NF-kB binding activity and inflammatory markers (IL-6, hsCRP) were analyzed at baseline and after eight weeks of treatment. NF-kB binding activity was analyzed by electrophoretic mobility shift assay. IL-6 and hsCRP were measured by ELISA.

RESULTS: After eight weeks of treatment LDL-cholesterol was lowered to the same extent in both treatment groups (p = 0.40) but not in placebo. However, patients taking sim80 showed a significant reduction of mononuclear NF-kB binding activity compared to baseline (p = 0.009) while no effect was observed in the sim10eze10 group (p = 0.79). Similar differences in anti-inflammatory effects were also observed when analyzing hsCRP (sim80: p = 0.03; sim10eze10: p = 0.40) and IL-6 levels (sim80: p = 0.15;

sim10eze10: $p = 0.95$).

CONCLUSION: High dose simvastatin therapy reduces proinflammatory transcription factor NF- κ B binding activity and hsCRP levels, while combination of low dose simvastatin with ezetimibe resulting in a similar LDL-reduction does not affect these inflammatory markers. Copyright 2012 Elsevier Ireland Ltd. All rights reserved.

Ruggenti, P., D. Cattaneo, et al. (2010). "Effects of combined ezetimibe and simvastatin therapy as compared with simvastatin alone in patients with type 2 diabetes: a prospective randomized double-blind clinical trial." *Diabetes Care* **33**(9): 1954-6.

OBJECTIVE: To assess the effects of inhibited gastrointestinal cholesterol absorption in statin-treated dyslipidemic patients. **RESEARCH DESIGN AND METHODS:** In a multicenter prospective randomized double-blind placebo-controlled trial, we primarily compared by ANCOVA the effect of 2-month ezetimibe (10 mg/day) or placebo therapy on LDL cholesterol serum levels in 108 type 2 diabetic patients with albuminuria <200 microg/min and total cholesterol concentrations >135 mg/dl despite simvastatin treatment (40 mg/day). **RESULTS:** Unlike placebo, ezetimibe decreased LDL cholesterol from 99 ± 31 to 66 ± 22 mg/dl, total cholesterol from 162 ± 36 to 124 ± 30 mg/dl, and apolipoprotein B from 83 ± 22 to 64 ± 18 mg/dl ($P < 0.0001$ for all changes versus placebo). A total of 72 and 17% of patients on ezetimibe or placebo achieved LDL levels <70 mg/dl, respectively ($P < 0.0001$). Treatment was well tolerated. **CONCLUSIONS:** Adding ezetimibe to simvastatin therapy helps to improve the pro-atherogenic lipoprotein profile in type 2 diabetic patients who fail to reach recommended lipid targets with statin therapy alone.

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.

Sansanayudh, N., S. Wongwiwatthananukit, et al. (2010). "Comparative efficacy and safety of low-dose pitavastatin versus atorvastatin in patients with hypercholesterolemia." Annals of Pharmacotherapy **44**(3): 415-23.

BACKGROUND: Previous studies have shown conflicting results on low-density lipoprotein cholesterol (LDL-C) reduction for comparable doses of pitavastatin and atorvastatin. **OBJECTIVE:** To compare the efficacy of pitavastatin 1 mg once daily with that of atorvastatin 10 mg once daily on lipoprotein change, safety, and cost per percent LDL-C reduction. **METHODS:** An 8-week, randomized, open-label, parallel trial was conducted in patients with hypercholesterolemia. One hundred patients were equally randomized to receive pitavastatin 1 mg once daily or atorvastatin 10 mg once daily; 98 completed the study. Outcomes were assessed at baseline and at the end of the study. **RESULTS:** Pitavastatin lowered LDL-C levels from baseline by 37% compared with 46% in the atorvastatin group ($p < 0.001$). The reduction of total cholesterol (TC) levels from baseline was significantly different between the pitavastatin (28%) and atorvastatin (32%) groups ($p = 0.005$). There was no significant difference in the percentage of changes in triglyceride and high-density lipoprotein cholesterol levels between groups. The percentage of patients who achieved LDL-C goals according to National Cholesterol Education Program-Adult Treatment Panel III guidelines was not significantly different between the pitavastatin (74%) and atorvastatin (84%) groups ($p = 0.220$). In addition, both regimens were well tolerated, with no patient developing an elevation of more than 3 times the upper normal limit of alanine aminotransferase or 10 times that of creatine kinase. The monthly cost per percent LDL-C reduction in the pitavastatin group (\$0.77) was about 50% lower than the cost in the atorvastatin (\$1.56) group. **CONCLUSIONS:** Although pitavastatin 1 mg daily was not as effective at lowering LDL-C and TC levels as atorvastatin 10 mg daily, the number of patients achieving their LDL-C goals with pitavastatin was comparable with the number using atorvastatin. Pitavastatin 1 mg once daily may be an alternative regimen with cost-saving benefits but without a significant decrease in therapeutic benefit or increase in adverse events in patients with hypercholesterolemia.

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 MyocAr dial 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.

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 atorvastatin 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-naïve 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.

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.

Stender, S., D. Budinski, et al. (2013). "Pitavastatin demonstrates long-term efficacy, safety and tolerability in elderly patients with primary hypercholesterolaemia or combined (mixed) dyslipidaemia." European Journal of Preventive Cardiology 20(1): 29-39.

AIMS: To assess the long-term efficacy, safety and tolerability of pitavastatin (2 and 4 mg) in elderly patients (≥ 65 years of age) with primary hypercholesterolaemia or combined (mixed) dyslipidaemia.

DESIGN: Patients (n = 545) who had completed a 12-week double-blind comparative study (core study) of pitavastatin and pravastatin entered a 60-week, open-label, multicentre extension study of pitavastatin. The initial daily dose was 2 mg, increasing to 4 mg after 8 weeks if necessary to achieve treatment targets. The proportion of patients attaining European Atherosclerosis Society (EAS) and National Cholesterol Education Program Adult Treatment Plan III (NCEP ATP III) targets for low-density lipoprotein cholesterol (LDL-C) was determined.

RESULTS: Of the patients enrolled, 539 received at least one dose of pitavastatin (safety population: men, 45.5%; Caucasian, 99.1%; mean age, 70.3 years; range, 65-89 years). Only 17% of patients required up-titration to pitavastatin 4 mg. After 60 weeks, NCEP ATP III and EAS targets were attained by 93.8% and 89.0% of patients, respectively. Plasma LDL-C declined by 43.4% and high-density lipoprotein cholesterol increased by 9.6% versus core-study baseline values. Pitavastatin was well tolerated: the most

common treatment-emergent adverse events were nasopharyngitis, mild/moderate myalgia and hypertension. There were no cases of severe myalgia, myopathy, myositis or rhabdomyolysis, and no significant findings on urinalysis, vital signs or 12-lead ECG.

CONCLUSION: Long-term pitavastatin treatment (2 and 4 mg) is effective in lowering LDL-C levels and has a good safety and tolerability profile in elderly patients.

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 \geq 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. Copyright 2011 Japanese College of Cardiology. Published by Elsevier Ltd. All rights reserved.

Undas, A., A. Machnik, et al. (2011). "Ezetimibe combined with simvastatin compared with simvastatin alone results in a greater suppression of oxidative stress and enhanced fibrinolysis in patients after acute coronary events." Journal of Cardiovascular Pharmacology 58(2): 167-172.

We compared the effect of simvastatin versus simvastatin combined with ezetimibe on

hemostasis and inflammation after acute coronary events [acute coronary syndromes (ACS)]. In an investigator-initiated, double-blind, placebo-controlled, randomized study, patients with ACS were assigned to 40 mg/d of simvastatin + 10 mg/d of ezetimibe (n = 26) or 40 mg/d of simvastatin + placebo (n = 28) administered for 2 months. Markers of coagulation (prothrombin fragments 1.2, thrombin-antithrombin complexes, free tissue factor pathway inhibitor), fibrinolysis [plasminogen activator inhibitor-1, clot lysis time (CLT)], platelet activation (soluble CD40 ligand, -thromboglobulin, thromboxane B2), oxidative stress [8-iso-prostaglandin F2 (8-iso-PGF2)], and inflammation (interleukin-6, interleukin-18, and interleukin-1) were measured within the first 12 hours of ACS and at 1 and 2 months of therapy. A final analysis comprised 20 patients in the simvastatin + ezetimibe group and 26 patients in the simvastatin + placebo group. Both groups were similar with regard to demographics, risk factors, medications, and routine laboratory results. Inflammatory, coagulation, and platelet markers did not differ between both treatment groups at all time points. Reductions in low-density lipoprotein cholesterol, CLT, plasminogen activator inhibitor-1, and 8-iso-PGF2 were significantly greater (by 10%, 8.7%, 17.5%, and 22.4%) in the simvastatin + ezetimibe group after 1 month, with further decreases in CLT and 8-iso-PGF2 at 2 months (all $P < 0.05$). These changes were not associated with lipid and inflammatory parameters. In conclusion, compared with simvastatin alone, simvastatin + ezetimibe results in a greater suppression of oxidative stress and enhanced fibrinolysis in patients with ACS, indicating that ezetimibe might exert cholesterol-independent actions in humans (NCT00725829).

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-naïve 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 cm³), $p = \text{NS}$) or S (11.0 +/- 1.5-10.5 +/- 1.4 cm³), $p = \text{NS}$). 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-naïve 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. Copyright 2011 Elsevier Ireland Ltd. All rights reserved.

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] \geq 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.

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.

Yoshida, H., T. Shoda, et al. (2013). "Effects of pitavastatin and atorvastatin on lipoprotein oxidation biomarkers in patients with dyslipidemia." *Atherosclerosis* 226(1): 161-164.

OBJECTIVE: The effects of potent statins on oxidized lipoprotein biomarkers are not well defined.

METHODS AND RESULTS: The VISION (Value of oxidant lipid lowering effect by Statin InterventiON in hypercholesterolemia) Trial randomized patients with hypercholesterolemia to 12-week administration of pitavastatin 2mg/day (n=21) or atorvastatin 10mg/day (n=21) and a variety of lipoprotein oxidative biomarkers were measured. Between-group analysis did not reveal any differences except in the ratio of malondialdehyde (MDA)-LDL over apolipoprotein B-100 (MDA-LDL/apoB) in pitavastatin vs. atorvastatin group (-13% vs.-0.7%, p=0.04). Within-group changes from baseline to 12-week revealed significant increases in OxPL/apoB and reductions in small-dense LDL, MDA-LDL, and lipoprotein-associated phospholipase A(2) measured on circulating apoB particles (Lp-PLA(2)/apoB) in both groups and significant reductions in OxPL/apoAI in the atorvastatin group.

CONCLUSIONS: The VISION study describes the first comparison on lipoprotein oxidation biomarkers between pitavastatin and atorvastatin and suggests diverse effects on lipoprotein oxidation markers in patients with hypercholesterolemia. Copyright 2012 Elsevier Ireland Ltd. All rights reserved.