

Drug Class Review on HMG-CoA Reductase Inhibitors (Statins)

Update #6: Preliminary Scan Report

December 2007

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. 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.

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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 only to assist with Participating Organizations' consideration of allocating resources toward a full update of this topic. Comprehensive review, quality assessment and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the FDA or Health Canada since the last report. Other important studies could exist.

Date of Last Update Report

August 2006 (searches through March 2006)

Date of last Preliminary Update Scan

November 2006

Scope and Key Questions

The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project. 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 clinicians, patients. The participating organizations approved the following key questions to guide this review:

1. How do statins compare in their ability to reduce LDL-c?
 - a. Are there doses for each statin that produce similar percent reduction in LDL-c between statins?
 - b. Is there a difference in the ability of a statin to achieve National Cholesterol Education Panel (NCEP) goals?
2. How do statins compare in their ability to raise HDL-c?
3. How do statins compare in their ability to reduce the risk of nonfatal myocardial infarction, CHD (angina), CHD mortality, all-cause mortality, stroke, or need for revascularization (coronary artery bypass graft, angioplasty, or stenting)?
4. Are there differences in the
 - a. Effectiveness of statins in different demographic groups (age, sex, race)?
 - b. Safety of statins in different demographic groups?
5. Are there differences in the safety of statins
 - a. In the general population
 - b. When used in special populations or with other medications (drug-drug interactions)? In addressing this question, we focused on the following populations and adverse effects:

- i. Patients with diabetes
- ii. Patients with HIV
- iii. Organ transplant recipients
- iv. Patients at high risk for myotoxicity
- v. Patients at high risk for hepatotoxicity
- vi. Patients using fibrates (gemfibrozil, fenofibrate) or niacin

The choice of key questions reflects the view that the following criteria may be used to select a statin: (1) the ability to lower LDL-c, (2) the ability to raise HDL-c, (3) the amount of information on cardiovascular outcomes available for each statin, (4) adverse effects, and (5) effects in demographic subgroups and in patients with concurrent medical conditions and drug therapies.

Included populations

Eligible populations consisted of adults (age ≥ 18 years) targeted for primary or secondary prevention of CHD or non-coronary forms of atherosclerotic disease with or without hypercholesterolemia. We excluded trials focusing on children and on rare, severe forms of hypercholesterolemia (LDL-c ≥ 250 mg/dl). We included trials in inpatients with acute coronary syndrome and trials of patients undergoing revascularization if the statin was continued after hospital discharge and if health outcomes were reported.

Included interventions

Trials of atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and/or simvastatin were included. We included studies that used one of three different strategies for dosing: fixed doses, single-dose titration, or treat (titrate dose) to a target LDL-c. We excluded multi-interventional therapies where the effect of the statin could not be separated out.

Included outcomes

For clinical efficacy, we included studies that reported one or more of the following as primary, secondary, or incidentally reported outcomes:

Intermediate outcome measures. LDL-c reduction or the percent of patients meeting NCEP goals; HDL-c raising.

Health outcomes. Nonfatal myocardial infarction, angina, cardiovascular death, all-cause mortality, stroke, and need for revascularization (coronary artery bypass graft, angioplasty, and stenting).

We excluded studies that did not provide original data (e.g., editorials, letters), were shorter than 4 weeks in duration, did not have an English-language title or abstract, or were published only in abstract form.

We used head-to-head trials to compare the efficacy and adverse effects of different statins in a defined population. Most head-to-head trials compare the short-term effects of different statins on LDL-c and HDL-c and on adverse events. Long-term head-to-head trials were scarce, so we relied heavily on placebo-controlled single drug trials to determine which statins have been proven to reduce mortality and the incidence of cardiovascular events. We

used randomized trials as well as observational cohort studies to estimate the incidence of complications of statin therapy such as rhabdomyolysis as well as the incidence of elevations in liver enzymes or creatinine phosphokinase levels. For drug interactions, we also included observational studies and individual case reports, because patients who are receiving drugs with a potential for interaction are often excluded from clinical trials. Although they do not provide comparative data, case reports were included because they may provide insight into more rare, significant interactions.

All titles and, if available, abstracts were reviewed for eligibility using the above criteria. Full-text articles of included titles and abstracts were retrieved and a second review for eligibility was conducted.

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE, Ovid MEDLINE Daily Update, and Ovid MEDLINE In-Process & Other Non-Indexed Citations from October 2006 through November Week 1 2007 using terms for included drugs. We also searched FDA (<http://www.fda.gov/medwatch/safety.htm>) and Health Canada (http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2007/index_e.html) websites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote 9.0) and duplicate citations were removed.

Study Selection

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

RESULTS

Overview

Searches resulted in 178 citations. Of those, there are 20 potentially relevant new trials (see Appendix A for abstracts).

Six new trials measured lipids:

Study, year	Comparison	Population
Asztalos, 2007	atorvastatin vs rosuvastatin	Hyperlipidemia
Deedwania, 2007b	atorvastatin vs rosuvastatin	South-Asian origin
Ferdinand, 2006	atorvastatin vs rosuvastatin	African Americans
Insull, 2007	atorvastatin vs rosuvastatin vs simvastatin	High-risk for CHD
Pearson, 2007	atorvastatin vs simvastatin	Hyperlipidemia
Bonnet, 2007	pravastatin vs placebo	HIV-infected

Five new trials reported health outcomes:

Study	Design	Primary outcome	Comparison	Population
Amarenco, 2006	Placebo	Stroke	atorvastatin	Recent stroke or TIA
Knopp, 2006	Placebo	Composite of cardiovascular endpoints	atorvastatin	Type 2 diabetes
Nakamura, 2006	Placebo	Primary prevention of cardiovascular disease	pravastatin	Japanese patients with hyperlipidemia
Wojnicz, 2006	Statin vs standard care	Heart failure symptoms	atorvastatin	Heart failure and elevated cholesterol
Deedwania, 2007a	Head-to-head	Ischemia	atorvastatin 80 mg vs pravastatin 40 mg (intensive vs moderate lipid lowering)	Elderly; CAD or prior MI

Nine studies reported new secondary or subgroup analyses of trials previously published:

Study	Trial	Primary outcome	Comparison	Population
Wenger, 2007	Treating to New Targets (TNT)	CV outcomes in patients age 65 and older	atorvastatin 10 mg vs 80 mg	Secondary analysis of elderly, stable CHD
Khush, 2007	TNT	Hospitalization for heart failure	atorvastatin 10 mg vs 80 mg	Stable coronary disease
LaRosa, 2007	TNT	First major CV event	atorvastatin 10 mg vs 80 mg	Secondary analysis of patients achieving very low LDL levels
Murphy, 2007	Patient-level meta-analysis of A to Z and Prove-IT trials	Mortality	atorvastatin vs pravastatin (high-dose vs standard dose therapy)	Acute coronary syndrome
Chonchol, 2007	4S	All-cause mortality and major coronary events	simvastatin vs placebo	Mild chronic renal insufficiency
Fellstrom, 2006	ALERT	Renal function	fluvastatin vs placebo	Renal transplant recipients
HPS Study Collaborative,	Heart Protection	Major vascular events	simvastatin vs placebo	Peripheral artery disease

Study	Trial	Primary outcome	Comparison	Population
2007	Study			
Olsson, 2007	MIRACL	CV outcomes in older vs younger patients	atorvastatin vs placebo	Elderly, acute coronary syndrome
Ford, 2007	WOSCOPS	Deaths, hospitalizations, cancer (5-year followup)	pravastatin vs placebo	Men with hyperlipidemia

New Drugs

No new drugs were identified.

New Indications

Atorvastatin (March 2007): Received new indications, based on the results of the Treating to New Targets Study (TNT), for the use of atorvastatin in adult patients with clinically evident coronary heart disease to reduce the risk of non-fatal myocardial infarction, fatal and non-fatal stroke, angina, revascularization procedures, and hospitalization for congestive heart failure.

Rosuvastatin (November 2007): Received a new indication for slowing the progression of atherosclerosis as part of a treatment strategy to lower total-C and LDL-C as an adjunct to diet.

New Safety Alerts

No new safety alerts for included drugs were identified.

Appendix A. Abstracts of potentially relevant new trials of statins

Amarenco, P., J. Bogousslavsky, et al. (2006). "High-dose atorvastatin after stroke or transient ischemic attack.[see comment]." *New England Journal of Medicine* **355**(6): 549-59.

BACKGROUND: Statins reduce the incidence of strokes among patients at increased risk for cardiovascular disease; whether they reduce the risk of stroke after a recent stroke or transient ischemic attack (TIA) remains to be established. **METHODS:** We randomly assigned 4731 patients who had had a stroke or TIA within one to six months before study entry, had low-density lipoprotein (LDL) cholesterol levels of 100 to 190 mg per deciliter (2.6 to 4.9 mmol per liter), and had no known coronary heart disease to double-blind treatment with 80 mg of atorvastatin per day or placebo. The primary end point was a first nonfatal or fatal stroke. **RESULTS:** The mean LDL cholesterol level during the trial was 73 mg per deciliter (1.9 mmol per liter) among patients receiving atorvastatin and 129 mg per deciliter (3.3 mmol per liter) among patients receiving placebo. During a median follow-up of 4.9 years, 265 patients (11.2 percent) receiving atorvastatin and 311 patients (13.1 percent) receiving placebo had a fatal or nonfatal stroke (5-year absolute reduction in risk, 2.2 percent; adjusted hazard ratio, 0.84; 95 percent confidence interval, 0.71 to 0.99; $P=0.03$; unadjusted $P=0.05$). The atorvastatin group had 218 ischemic strokes and 55 hemorrhagic strokes, whereas the placebo group had 274 ischemic strokes and 33 hemorrhagic strokes. The five-year absolute reduction in the risk of major cardiovascular events was 3.5 percent (hazard ratio, 0.80; 95 percent confidence interval, 0.69 to 0.92; $P=0.002$). The overall mortality rate was similar, with 216 deaths in the atorvastatin group and 211 deaths in the placebo group ($P=0.98$), as were the rates of serious adverse events. Elevated liver enzyme values were more common in patients taking atorvastatin. **CONCLUSIONS:** In patients with recent stroke or TIA and without known coronary heart disease, 80 mg of atorvastatin per day reduced the overall incidence of strokes and of cardiovascular events, despite a small increase in the incidence of hemorrhagic stroke. (ClinicalTrials.gov number, NCT00147602 [ClinicalTrials.gov]). Copyright 2006 Massachusetts Medical Society.

Asztalos, B. F., F. Le Maulf, et al. (2007). "Comparison of the effects of high doses of rosuvastatin versus atorvastatin on the subpopulations of high-density lipoproteins." *American Journal of Cardiology* **99**(5): 681-5.

Atorvastatin and rosuvastatin are both highly effective in decreasing low-density lipoprotein cholesterol and triglyceride levels. However, rosuvastatin was shown to be more effective in increasing high-density lipoprotein (HDL) cholesterol levels. The purpose of the study is to compare the effects of daily doses of rosuvastatin 40 mg with atorvastatin 80 mg during a 6-week period on HDL subpopulations in 306 hyperlipidemic men and women. We previously showed that increased levels of large alpha-1 and alpha-2 HDLs decrease the risk of coronary heart disease and protect against progression of coronary atherosclerosis (superior to HDL cholesterol). In this study, both statins caused significant increases in large alpha-1 ($p < 0.001$) and alpha-2 ($p < 0.001$ for rosuvastatin, $p < 0.05$ for atorvastatin) and significant ($p < 0.001$) decreases in small pre-beta-1 HDL levels; however, increases in the 2 large HDL particles were significantly higher for rosuvastatin than atorvastatin (alpha-1, 24% vs 12%; alpha-2, 13% vs 4%; $p < 0.001$). Statin-induced increases in alpha-1 and alpha-2 correlated with increases in HDL cholesterol, whereas decreases in pre-beta-1 were associated with decreases in triglycerides. In subjects with low HDL cholesterol (< 40 mg/dl for men, < 50 mg/dl for women, $n = 99$), increases in alpha-1 were 32% versus 11%, and in alpha-2, 21% versus 5% for rosuvastatin and atorvastatin, respectively. In conclusion, our data show that both statins, given at their maximal doses, favorably alter the HDL subpopulation profile, but also that rosuvastatin is significantly more effective in this regard than atorvastatin.

Bonnet, F., V. Aurillac-Lavignolle, et al. (2007). "Pravastatin in HIV-infected patients treated with protease inhibitors: a placebo-controlled randomized study." HIV Clinical Trials **8**(1): 53-60.

PURPOSE: The objectives of the study were to assess the effects of pravastatin on plasma HIV RNA, lipid parameters, and protease inhibitor (PI) concentrations in patients treated with PI-containing regimens and with total cholesterol (TC) \geq 5.5 mmol/L. **METHOD:** A clinical trial including patients randomized to receive pravastatin or matching placebo for 12 weeks was implemented. **RESULTS:** Twelve patients were included in the pravastatin group and 9 in the placebo group. At week 12 (W12), no patient had experienced virological failure. Between week 0 (W0) and W12, the median differences for TC were -1.4 mmol/L in the pravastatin group and +0.2 mmol/L in the placebo group ($p = .005$); for LDL, they were -1.0 mmol/L and +0.3 ($p = .007$), respectively. A significant decrease of the PI concentration (12 hours after administration) ratio W12 - W0/W0 was noticed in the pravastatin group (-0.2 [interquartile range, -0.3 to -0.1] as compared with the placebo group (0.1 [IQR, 0.0 to 0.3]) ($p = .03$). When the study was restricted to patients treated with lopinavir/ritonavir, a decrease from 3.8 microg/mL at baseline to 2.9 mug/mL at W12 was noticed in the pravastatin arm ($p = .04$) but not in the control arm ($p = 1.00$). No clinical adverse event reached a severity of grade 3. **CONCLUSION:** We observed in this study that the use of pravastatin in PI-treated patients was not associated with major change in the plasma HIV RNA on 12 weeks of follow-up. However, we found a trend of decrease of the trough PI concentration at W12, suggesting a possible drug-drug interaction of pravastatin on PI metabolism.

Chonchol, M., T. Cook, et al. (2007). "Simvastatin for secondary prevention of all-cause mortality and major coronary events in patients with mild chronic renal insufficiency." American Journal of Kidney Diseases **49**(3): 373-82.

BACKGROUND: A potentially modifiable risk factor for cardiovascular disease in patients with mild chronic renal insufficiency is dyslipidemia. Few studies examined the effects of statins on all-cause mortality and major coronary events in patients with renal dysfunction. **METHODS:** We performed a post hoc analysis from the Randomized Trial of Cholesterol Lowering in 4,444 Patients with Coronary Heart Disease: The Scandinavian Simvastatin Survival Study. Of 4,444 participants, 2,314 (52.1%) had mild chronic renal insufficiency defined as an estimated glomerular filtration rate less than 75 mL/min/1.73 m² (<1.25 mL/s), measured using the Modification of Diet in Renal Disease equation. The primary end point was all-cause mortality. **RESULTS:** During the follow-up period, simvastatin use was associated with decreased all-cause mortality (adjusted hazard ratio [HR], 0.69; confidence interval [CI], 0.54 to 0.89) in the 2,314 participants with mild chronic renal insufficiency. Rates of major coronary events (adjusted HR, 0.67; CI, 0.56 to 0.79) and coronary revascularization (adjusted HR, 0.62; CI, 0.49 to 0.77) also were significantly lower in the simvastatin group. No significant decreases in stroke incidence were observed in the simvastatin group (adjusted HR, 0.88; CI, 0.55 to 1.39). The side-effect profile was similar between the 2 treatment groups. **CONCLUSION:** Simvastatin therapy appears to be effective and safe for the secondary prevention of all-cause mortality and major coronary events in patients with mild chronic renal dysfunction.

Deedwania, P., P. H. Stone, et al. (2007a). "Effects of intensive versus moderate lipid-lowering therapy on myocardial ischemia in older patients with coronary heart disease: results of the Study Assessing Goals in the Elderly (SAGE).[see comment]." Circulation **115**(6): 700-7.

BACKGROUND: Clinical trials have demonstrated that, compared with placebo, intensive statin therapy reduces ischemia in patients with acute coronary syndromes and in patients with stable coronary artery disease. However, no studies to date have assessed intensive versus moderate statin therapy in older patients with stable coronary syndromes. **METHODS AND RESULTS:** A total of 893 ambulatory coronary artery disease patients (30% women) 65 to 85 years of age with \geq 1 episode of myocardial ischemia that lasted \geq 3 minutes during 48-hour ambulatory

ECG at screening were randomized to atorvastatin 80 mg/d or pravastatin 40 mg/d and followed up for 12 months. The primary efficacy parameter (absolute change from baseline in total duration of ischemia at month 12) was significantly reduced in both groups at month 3 and month 12 (both $P < 0.001$ for each treatment group) with no significant difference between the treatment groups. Atorvastatin-treated patients experienced greater low-density lipoprotein cholesterol reductions than did pravastatin-treated patients, a trend toward fewer major acute cardiovascular events (hazard ratio, 0.71; 95% confidence interval, 0.46, 1.09; $P = 0.114$), and a significantly greater reduction in all-cause death (hazard ratio, 0.33; 95% confidence interval, 0.13, 0.83; $P = 0.014$). **CONCLUSIONS:** Compared with moderate pravastatin therapy, intensive atorvastatin therapy was associated with reductions in cholesterol, major acute cardiovascular events, and death in addition to the reductions in ischemia observed with both therapies. The contrast between the therapies' differing efficacy for major acute cardiovascular events and death and their nonsignificant difference in efficacy for reduction of ischemia suggests that low-density lipoprotein cholesterol-lowering thresholds for ischemia and major acute cardiovascular events may differ. The Study Assessing Goals in the Elderly (SAGE) demonstrates that older men and women with coronary artery disease benefit from intensive statin therapy.

Deedwania, P. C., M. Gupta, et al. (2007b). "Comparison of rosuvastatin versus atorvastatin in South-Asian patients at risk of coronary heart disease (from the IRIS Trial)." *American Journal of Cardiology* **99**(11): 1538-43.

In a large randomized trial of statin therapy in patients of South-Asian origin with hypercholesterolemia, 740 patients in the United States and Canada received 6 weeks of treatment with rosuvastatin 10 or 20 mg or atorvastatin 10 or 20 mg. A total of 485 patients (66%) were categorized as being at high risk of coronary heart disease and had a National Cholesterol Education Program Adult Treatment Panel III treatment goal of low-density lipoprotein (LDL) cholesterol < 100 mg/dl (< 2.6 mmol/L). LDL cholesterol decreased by 45% with rosuvastatin 10 mg versus 40% with atorvastatin 10 mg ($p = 0.0023$) and by 50% with rosuvastatin 20 mg versus 47% with atorvastatin 20 mg ($p = \text{NS}$). National Cholesterol Education Program Adult Treatment Panel III LDL cholesterol goal achievement rates in high-risk patients (all patients) were 76% (79%) and 88% (89%) with rosuvastatin 10 and 20 mg, respectively, compared with 70% (76%) and 81% (85%) with atorvastatin 10 and 20 mg, respectively. Rosuvastatin and atorvastatin were well tolerated. There were no clinically relevant differences between statins in adverse events or incidence of creatine kinase > 10 times the upper limit of normal, alanine aminotransferase > 3 times the upper limit of normal on 2 consecutive occasions, or proteinuria or hematuria over the relatively short duration of treatment. In conclusion, statin therapy was well tolerated and effective in decreasing LDL cholesterol in patients of South-Asian origin, with the 10- and 20-mg doses of rosuvastatin and atorvastatin allowing most patients to reach recommended LDL cholesterol goals.

Fellstrom, B., S. Abedini, et al. (2006). "No detrimental effect on renal function during long-term use of fluvastatin in renal transplant recipients in the Assessment of Lescol in Renal Transplantation (ALERT) study." *Clinical Transplantation* **20**(6): 732-9.

BACKGROUND: Concerns have recently been raised regarding a potential harmful effect of statins on renal function. This study investigated the effect of fluvastatin treatment on renal function in renal transplant recipients enrolled in the Assessment of Lescol in Renal Transplantation (ALERT) trial. **METHODS:** ALERT was a randomized, double-blind, placebo-controlled study of the effect of fluvastatin, 40-80 mg daily ($n = 1050$) or placebo ($n = 1052$) on cardiac and renal outcomes in renal transplant recipients over a follow-up period of five to six years. The incidence of graft loss, changes in serum creatinine, calculated creatinine clearance and proteinuria, and the incidence of renal adverse events (AEs) were assessed in both treatment groups. **RESULTS:** Fluvastatin treatment in ALERT had no significant effect compared with

placebo on renal function, assessed by serum creatinine (overall adjusted mean +/- SEM: fluvastatin, 175.4 +/- 2.20 micromol/L; placebo, 172.7 +/- 2.20 micromol/L; p = 0.39), creatinine clearance (fluvastatin, 55.3 +/- 0.30 mL/min; placebo, 55.8 +/- 0.30 mL/min; p = 0.26) or proteinuria (fluvastatin, 0.58 +/- 0.03 g/24 h; placebo, 0.53 +/- 0.03 g/24 h; p = 0.31). There were no significant differences between treatment groups when the 283 patients suffering graft loss were excluded from the analysis. Fluvastatin also had no detrimental effect on creatinine clearance or proteinuria in the subgroup of 340 diabetic patients without graft loss in ALERT. No notable differences in the rate of renal or musculoskeletal AEs were observed between fluvastatin and placebo groups. CONCLUSIONS: Fluvastatin had no detrimental effect on renal function, or the risk of renal AEs, in renal transplant recipients with or without diabetes enrolled in ALERT. Fluvastatin treatment for the prevention of cardiac events may therefore be used without fear of jeopardizing renal function.

Ferdinand, K. C., L. T. Clark, et al. (2006). "Comparison of efficacy and safety of rosuvastatin versus atorvastatin in African-American patients in a six-week trial.[see comment]." American Journal of Cardiology **97**(2): 229-35.

The lipid-modifying effects of statin therapy in hypercholesterolemic African-Americans have not been well characterized. This study compared the efficacy and safety of rosuvastatin and atorvastatin treatment for 6 weeks in hypercholesterolemic African-American adults. In the African American Rosuvastatin Investigation of Efficacy and Safety (ARIES) trial (4522US/0002), 774 adult African-Americans with low-density lipoprotein cholesterol \geq or = 160 and \leq or = 300 mg/dl and triglycerides $<$ 400 mg/dl were randomized to receive open-label rosuvastatin 10 or 20 mg or atorvastatin 10 or 20 mg for 6 weeks. At week 6, significantly greater reductions in low-density lipoprotein cholesterol, total cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B concentrations, as well as lipoprotein and apolipoprotein ratios, were seen with rosuvastatin versus milligram-equivalent atorvastatin doses (analysis of variance with Bonferroni-adjusted critical $p < 0.017$ for all comparisons). Rosuvastatin 10 mg also increased high-density lipoprotein cholesterol significantly more than atorvastatin 20 mg ($p < 0.017$). Although statistical comparisons were not performed, larger proportions of rosuvastatin-treated patients than atorvastatin-treated patients achieved National Cholesterol Education Program Adult Treatment Panel III low-density lipoprotein cholesterol goals. The median high-sensitivity C-reactive protein levels were significantly reduced statistically from baseline with rosuvastatin 20 mg and atorvastatin 20 mg among all patients and with rosuvastatin 10 and 20 mg and atorvastatin 20 mg in those patients with a baseline C-reactive protein level $>$ 2.0 mg/L. The 2 study medications were well tolerated during the 6-week study period. In conclusion, rosuvastatin 10 and 20 mg improved the overall lipid profile of hypercholesterolemic African-Americans better than did milligram-equivalent doses of atorvastatin.

Ford, I., H. Murray, et al. (2007). "Long-term follow-up of the West of Scotland Coronary Prevention Study.[see comment]." New England Journal of Medicine **357**(15): 1477-86.

BACKGROUND: The West of Scotland Coronary Prevention Study was a randomized clinical trial comparing pravastatin with placebo in men with hypercholesterolemia who did not have a history of myocardial infarction, with an average follow-up of approximately 5 years. The combined outcome of death from definite coronary heart disease or definite nonfatal myocardial infarction was reduced from 7.9 to 5.5% ($P < 0.001$) in the treatment group. Extended follow-up data were obtained for approximately 10 years after completion of the trial. METHODS: For the survivors of the trial, all deaths, hospitalizations and deaths due to coronary events and stroke, and incident cancers and deaths from cancer were tracked with the use of a national computerized record-linkage system. The results were analyzed with time-to-event analyses and use of Cox proportional-hazards models. RESULTS: Five years after the trial ended, 38.7% of the original statin group and 35.2% of the original placebo group were being treated with a statin. In the

period approximately 10 years after completion of the trial, the risk of death from coronary heart disease or nonfatal myocardial infarction was 10.3% in the placebo group and 8.6% in the pravastatin group ($P=0.02$); over the entire follow-up period, the rate was 15.5% in the placebo group and 11.8% in the pravastatin group ($P<0.001$). Similar percentage reductions were seen in the combined rate of death from coronary heart disease and hospitalization for coronary events for both periods. The rate of death from cardiovascular causes was reduced ($P=0.01$), as was the rate of death from any cause ($P=0.03$), over the entire follow-up period. There were no excess deaths from noncardiovascular causes or excess fatal or incident cancers. **CONCLUSIONS:** In this analysis, 5 years of treatment with pravastatin was associated with a significant reduction in coronary events for a subsequent 10 years in men with hypercholesterolemia who did not have a history of myocardial infarction. Copyright 2007 Massachusetts Medical Society.

Heart Protection Study Collaborative, G. (2007). "Randomized trial of the effects of cholesterol-lowering with simvastatin on peripheral vascular and other major vascular outcomes in 20,536 people with peripheral arterial disease and other high-risk conditions." *Journal of Vascular Surgery* **45**(4): 645-654; discussion 653-4.

OBJECTIVES: The Heart Protection Study (HPS) provides an opportunity to assess directly the effects of cholesterol-lowering therapy on major vascular events (defined as myocardial infarction, coronary death, stroke, or revascularization) in patients with peripheral arterial disease (PAD). In addition, the effects on peripheral vascular events (ie, non-coronary revascularization, aneurysm repairs, major amputations or PAD deaths) can be assessed. **METHODS:** 6748 UK adults with PAD and 13,788 other high-risk participants were randomly allocated to receive 40 mg simvastatin daily or matching placebo, yielding an average LDL cholesterol difference of 1.0 mmol/L (39 mg/dL) during a mean of 5 years. **RESULTS:** For participants with PAD, allocation to simvastatin was associated with a highly significant 22% (95% CI 15-29) relative reduction in the rate of first major vascular event following randomisation (895 [26.4%] simvastatin-allocated vs 1101 [32.7%] placebo-allocated; $P < .0001$), which was similar to that seen among the other high-risk participants. The absolute reduction in first major vascular event was 63 (SE 11) per 1000 patients with PAD and 50 (SE 7) per 1000 without pre-existing PAD. Overall, among all participants, there was a 16% (5-25) relative reduction in the rate of first peripheral vascular event following randomisation (479 [4.7%] simvastatin vs 561 [5.5%] placebo), largely irrespective of baseline LDL cholesterol and other factors. This effect chiefly reflects a 20% (8-31) relative reduction in non-coronary revascularization procedures (334 [3.3%] vs 415 [4.0%]; $P = .002$). **CONCLUSION:** HPS demonstrates the benefits of cholesterol-lowering statin therapy in patients with PAD, regardless of their presenting cholesterol levels and other presenting features. Allocation to 40 mg simvastatin daily reduces the rate of first major vascular events by about one-quarter, and that of peripheral vascular events by about one-sixth, with large absolute benefits seen in participants with PAD because of their high vascular risk. Consequently, statin therapy should be considered routinely for all patients with PAD.

Insull, W., Jr., J. K. Ghali, et al. (2007). "Achieving low-density lipoprotein cholesterol goals in high-risk patients in managed care: comparison of rosuvastatin, atorvastatin, and simvastatin in the SOLAR trial.[see comment]." *Mayo Clinic Proceedings* **82**(5): 543-50.

OBJECTIVE: To evaluate attainment of the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III low-density lipoprotein cholesterol (LDL-C) goal of less than 100 mg/dL with statin treatments in managed care patients at high risk for coronary heart disease. **PATIENTS AND METHODS:** In a randomized, open-label, multicenter trial (SOLAR [Satisfying Optimal LDL-C ATP III goals with Rosuvastatin]) performed at 145 US clinical centers from June 5, 2002 to July 12, 2004, high-risk men and women in a managed care population received typical starting doses of rosuvastatin (10 mg/d), atorvastatin (10 mg/d), or simvastatin (20 mg/d) for 6 weeks. Those who did not meet the LDL-C target of less than 100

mg/dL at 6 weeks had their dose titrated (doubled), and all patients were followed up for another 6 weeks. **RESULTS:** A total of 1632 patients were randomized to 1 of the 3 treatment regimens. After 6 weeks, 65% of patients taking rosuvastatin reached the LDL-C target of less than 100 mg/dL vs 41% with atorvastatin and 39% with simvastatin ($P < .001$ vs rosuvastatin for both). After 12 weeks, 76% of patients taking rosuvastatin reached the LDL-C target of less than 100 mg/dL vs 58% with atorvastatin and 53% with simvastatin ($P < .001$ vs rosuvastatin for both). Reductions in the LDL-C level, total cholesterol level, non-high-density lipoprotein cholesterol (non-HDL-C) level, and non-HDL-C/HDL-C ratio were significantly greater with rosuvastatin at both 6 and 12 weeks compared with the other statins. Adverse events were similar in type and frequency in all treatment groups, and only 3% of all patients discontinued treatment because of adverse events. No myopathy was observed, no clinically important impact on renal function was attributed to study medications, and clinically important increases in serum transaminases were rare. **CONCLUSION:** In a managed care population, 10 mg of rosuvastatin treatment resulted in more patients reaching the NCEP ATP III LDL-C goal compared with 10 mg of atorvastatin and 20 mg of simvastatin, potentially reducing the need for titration visits.

Khush, K. K., D. D. Waters, et al. (2007). "Effect of high-dose atorvastatin on hospitalizations for heart failure: subgroup analysis of the Treating to New Targets (TNT) study." *Circulation* **115**(5): 576-83. **BACKGROUND:** Statins reduce the rate of major cardiovascular events in high-risk patients, but their potential benefit as treatment for heart failure (HF) is less clear. **METHODS AND RESULTS:** Patients ($n=10,001$) with stable coronary disease were randomized to treatment with atorvastatin 80 or 10 mg/d and followed up for a median of 4.9 years. A history of HF was present in 7.8% of patients. A known ejection fraction $<30\%$ and advanced HF were exclusion criteria for the study. A predefined secondary end point of the study was hospitalization for HF. The incidence of hospitalization for HF was 2.4% in the 80-mg arm and 3.3% in the 10-mg arm (hazard ratio, 0.74; 95% confidence interval, 0.59 to 0.94; $P=0.0116$). The treatment effect of the higher dose was more marked in patients with a history of HF: 17.3% versus 10.6% in the 10- and 80-mg arms, respectively (hazard ratio, 0.59; 95% confidence interval, 0.4 to 0.88; $P=0.009$). Among patients without a history of HF, the rates of hospitalization for HF were much lower: 1.8% in the 80-mg group and 2.0% in the 10-mg group (hazard ratio, 0.87; 95% confidence interval, 0.64 to 1.16; $P=0.34$). Only one third of patients hospitalized for HF had evidence of preceding angina or myocardial infarction during the study period. Blood pressure was almost identical during follow-up in the treatment groups. **CONCLUSIONS:** Compared with a lower dose, intensive treatment with atorvastatin in patients with stable coronary disease significantly reduces hospitalizations for HF. In a post hoc analysis, this benefit was observed only in patients with a history of HF. The mechanism accounting for this benefit is unlikely to be due primarily to a reduction in interim coronary events or differences in blood pressure.

Knopp, R. H., M. d'Emden, et al. (2006). "Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN).[see comment]." *Diabetes Care* **29**(7): 1478-85.

OBJECTIVE: Cardiovascular disease (CVD) risk is increased in type 2 diabetes. The purpose of this study was to assess the effect of 10 mg of atorvastatin versus placebo on CVD prevention in subjects with type 2 diabetes and LDL cholesterol levels below contemporary guideline targets. **RESEARCH DESIGN AND METHODS:** Subjects were randomly assigned to receive 10 mg of atorvastatin or placebo in a 4-year, double-blind, parallel-group study. The composite primary end point comprised cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, revascularization, coronary artery bypass surgery, resuscitated cardiac arrest, and worsening or unstable angina requiring hospitalization. **RESULTS:** A total of 2,410 subjects with type 2 diabetes were randomized. Mean LDL cholesterol reduction in the atorvastatin group over 4 years

was 29% versus placebo ($P < 0.0001$). When we compared atorvastatin versus placebo, composite primary end point rates were 13.7 and 15.0%, respectively (hazard ratio 0.90 [95% CI 0.73-1.12]). In the subset of 1,905 subjects without prior myocardial infarction or interventional procedure, 10.4% of atorvastatin- and 10.8% of placebo-treated subjects experienced a primary end point (0.97 [0.74-1.28]). In the 505 subjects with prior myocardial infarction or interventional procedure, 26.2% of atorvastatin- and 30.8% of placebo-treated subjects experienced a primary end point (0.82 [0.59-1.15]). Relative risk reductions in fatal and nonfatal myocardial infarction were 27% overall ($P = 0.10$) and 19% ($P = 0.41$) and 36% ($P = 0.11$) for subjects without and with prior myocardial infarction or interventional procedure, respectively. **CONCLUSIONS:** Composite end point reductions were not statistically significant. This result may relate to the overall study design, the types of subjects recruited, the nature of the primary end point, and the protocol changes required because of changing treatment guidelines. For these reasons, the results of the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN) did not confirm the benefit of therapy but do not detract from the imperative that the majority of diabetic patients are at risk of coronary heart disease and deserve LDL cholesterol lowering to the currently recommended targets.

LaRosa, J. C., S. M. Grundy, et al. (2007). "Safety and efficacy of Atorvastatin-induced very low-density lipoprotein cholesterol levels in Patients with coronary heart disease (a post hoc analysis of the treating to new targets [TNT] study)." *American Journal of Cardiology* **100**(5): 747-52.

High-dose statin therapy has been demonstrated to provide incremental benefit when low-density lipoprotein (LDL) cholesterol concentrations are lowered well below recommended target levels. This secondary analysis of the Treating to New Targets (TNT) study was conducted to investigate whether the attainment of very low LDL cholesterol levels was associated with a further reduction in major cardiovascular events compared with higher LDL cholesterol concentrations and whether any incremental benefit was achieved without additional safety risk. Patients with coronary heart disease and LDL cholesterol levels <130 mg/dl (3.4 mmol/L) were randomized to therapy with atorvastatin 10 mg/day ($n = 5,006$) or 80 mg/day ($n = 4,995$). The primary end point was the occurrence of a first major cardiovascular event. Clinical outcomes and safety data were compared across on-treatment LDL cholesterol quintiles. There was a highly significant reduction in the rate of major cardiovascular events with descending achieved levels of on-treatment LDL cholesterol ($p < 0.0001$ for trend across LDL cholesterol). Analysis of individual components of the primary end point demonstrated similar results. Death from any cause and from noncardiovascular causes was lowest in patients with the lowest on-treatment LDL cholesterol levels. Cardiovascular deaths were also reduced with lower levels of on-treatment LDL cholesterol. There were no clinically important differences in adverse event rates across quintiles. Specifically, no increase in muscle complaints, suicide, hemorrhagic stroke, or cancer deaths was observed at the lowest LDL cholesterol levels. In conclusion, the present analysis adds support to the concept that for patients with established atherosclerotic cardiovascular disease, a further risk reduction without sacrifice of safety can be achieved by reducing LDL cholesterol to very low levels.

Murphy, S. A., C. P. Cannon, et al. (2007). "Effect of intensive lipid-lowering therapy on mortality after acute coronary syndrome (a patient-level analysis of the Aggrastat to Zocor and Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 trials)." *American Journal of Cardiology* **100**(7): 1047-51.

Compared with moderate lipid lowering with standard-dose statin therapy, intensive lipid lowering with high-dose statin therapy after acute coronary syndromes (ACS) significantly reduces cardiovascular events. However, the 2 trials of high-dose versus standard-dose statin therapy in patients with ACS, Aggrastat to Zocor (A to Z) and Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22 (PROVE-IT-TIMI

22), were not individually powered to evaluate the impact on mortality alone. In this study, a pooled, patient-level analysis of these trials of 8,658 post-ACS patients was performed to provide a more robust estimate of the impact of intensive statin therapy on mortality. By 8 months, achieved low-density lipoprotein levels were lower in the group with intensive statin therapy (median 64 mg/dl, interquartile range 51 to 81) than in the group with moderate statin therapy (median 87 mg/dl, interquartile range 71 to 107) ($p < 0.001$). All-cause mortality was significantly reduced in the group with intensive statin therapy compared with the group with moderate statin therapy (3.6% vs 4.9%, hazard ratio 0.77, 95% confidence interval 0.63 to 0.95, $p = 0.015$), without significant interaction by trial (interaction $p = 0.63$). The reduction in all-cause mortality with intensive statin therapy was consistent across key subgroups. In conclusion, in this analysis of >8,600 patients, intensive lipid lowering with high-dose statin therapy after ACS was associated with reduced mortality compared with moderate lipid lowering with standard-dose statin therapy. On the basis of these findings, 1 death was prevented for every 95 patients treated with high-dose statin therapy for 2 years. The results of this pooled analysis provide further evidence for early intensive statin therapy after ACS.

Nakamura, H., K. Arakawa, et al. (2006). "Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial.[see comment]." *Lancet* **368**(9542): 1155-63.

BACKGROUND: Evidence-based treatment for hypercholesterolaemia in Japan has been hindered by the lack of direct evidence in this population. Our aim was to assess whether evidence for treatment with statins derived from western populations can be extrapolated to the Japanese population. **METHODS:** In this prospective, randomised, open-labelled, blinded study, patients with hypercholesterolaemia (total cholesterol 5.69-6.98 mmol/L) and no history of coronary heart disease or stroke were randomly assigned diet or diet plus 10-20 mg pravastatin daily. The primary endpoint was the first occurrence of coronary heart disease. Statistical analyses were done by intention to treat. This trial is registered at ClinicalTrials.gov, number NCT00211705. **FINDINGS:** 3966 patients were randomly assigned to the diet group and 3866 to the diet plus pravastatin group. Mean follow-up was 5.3 years. At the end of study, 471 and 522 patients had withdrawn, died, or been lost to follow-up in the diet and diet plus pravastatin groups, respectively. Mean total cholesterol was reduced by 2.1% (from 6.27 mmol/L to 6.13 mmol/L) and 11.5% (from 6.27 mmol/L to 5.55 mmol/L) and mean LDL cholesterol by 3.2% (from 4.05 mmol/L to 3.90 mmol/L) and 18.0% (from 4.05 mmol/L to 3.31 mmol/L) in the diet and the diet plus pravastatin groups, respectively. Coronary heart disease was significantly lower in the diet plus pravastatin group than in the diet alone group (66 events vs 101 events; HR 0.67, 95% CI 0.49-0.91; $p=0.01$). There was no difference in the incidence of malignant neoplasms or other serious adverse events between the two groups. **INTERPRETATION:** Treatment with a low dose of pravastatin reduces the risk of coronary heart disease in Japan by much the same amount as higher doses have shown in Europe and the USA.

Olsson, A. G., G. G. Schwartz, et al. (2007). "Effects of high-dose atorvastatin in patients > or =65 years of age with acute coronary syndrome (from the myocardial ischemia reduction with aggressive cholesterol lowering [MIRACL] study)." *American Journal of Cardiology* **99**(5): 632-5.

After acute coronary syndromes (ACSs), older patients are particularly susceptible to early complications, including death and recurrent ACS. Lipid management guidelines do not differentiate elderly from younger patients, and lack of evidence for statin benefits in older patients has led to underutilization of statins in the elderly. The MIRACL study randomized 3,086 patients to 16 weeks of 80 mg/day of atorvastatin or placebo 24 to 96 hours after ACS and demonstrated significant decreases in the combined primary end point (nonfatal acute myocardial infarction, resuscitated cardiac arrest, recurrent symptomatic myocardial ischemia). This post hoc analysis compared benefits of 80 mg of atorvastatin in older (> or =65 years) versus younger (<65

years) patients. Event rates were approximately two- to threefold higher in older than in younger patients. Treatment-by-age heterogeneity testing indicated no difference in treatment effect by age for any of the primary or secondary end points, and relative risk decreases in the primary end point with atorvastatin versus placebo were similar in younger and older patients (22% vs 14%, respectively). The safety profile of atorvastatin was similar between the 2 age groups. In conclusion, these results and a greater immediate cardiovascular risk in older patients argue for early, intensive atorvastatin therapy as routine practice after ACS.

Pearson, T., C. Ballantyne, et al. (2007). "Comparison of effects of ezetimibe/simvastatin versus simvastatin versus atorvastatin in reducing C-reactive protein and low-density lipoprotein cholesterol levels." *American Journal of Cardiology* **99**(12): 1706-1713.

The lowering effects of ezetimibe/simvastatin combination therapy on low-density lipoprotein (LDL) cholesterol and high-sensitivity C-reactive protein (CRP) were compared with those of simvastatin or atorvastatin monotherapy in a large cohort of patients with primary hypercholesterolemia. To compare ezetimibe/simvastatin with simvastatin, data were combined from 3 identical, prospective 12-week trials in which patients were randomized to receive placebo; ezetimibe 10 mg; ezetimibe 10 mg added to simvastatin 10, 20, 40, or 80 mg; or simvastatin 10, 20, 40, or 80 mg. To compare ezetimibe/simvastatin with atorvastatin, data were analyzed from a phase III double-blind, active-controlled study in which patients were randomized equally to receive ezetimibe/simvastatin 10/10, 10/20, 10/40, or 10/80 mg or atorvastatin 10, 20, 40, or 80 mg for 6 weeks. When averaged across doses, ezetimibe/simvastatin produced significantly greater reductions compared with simvastatin alone in LDL cholesterol (52.5% vs 38.0%, respectively) and CRP levels (31.0% vs 14.3%, respectively). At each individual simvastatin dose, co-administration with ezetimibe produced significant further CRP reductions versus simvastatin alone. Ezetimibe/simvastatin was significantly more effective at lowering LDL cholesterol than atorvastatin when pooled across doses (53.4% vs 45.3%, respectively) and in each milligram-equivalent dose comparison. Reductions in CRP of similar magnitude were observed with ezetimibe/simvastatin and atorvastatin when averaged across doses and at each milligram-equivalent statin dose comparison. In conclusion, the lipid-modulating and anti-inflammatory effects of ezetimibe/simvastatin provide additional benefits not realized by statin monotherapy alone.

Wenger, N. K., S. J. Lewis, et al. (2007). "Outcomes of using high- or low-dose atorvastatin in patients 65 years of age or older with stable coronary heart disease.[summary for patients in Ann Intern Med. 2007 Jul 3;147(1):I32; PMID: 17606953]." *Annals of Internal Medicine* **147**(1): 1-9.

BACKGROUND: Increased life expectancy is associated with an increase in the burden of chronic cardiovascular disease. **OBJECTIVE:** To assess the efficacy and safety of high-dose atorvastatin in patients 65 years of age or older. **DESIGN:** A prespecified secondary analysis of the Treating to New Targets study, a randomized, double-blind clinical trial. **SETTING:** 256 sites in 14 countries participating in the Treating to New Targets study. **PARTICIPANTS:** 10,001 patients (3809 patients \geq 65 years of age) with coronary heart disease (CHD) and low-density lipoprotein cholesterol levels less than 3.4 mmol/L (<130 mg/dL). **INTERVENTION:** Patients were randomly assigned to receive atorvastatin, 10 or 80 mg/d. **MEASUREMENTS:** The primary end point was the occurrence of a first major cardiovascular event (death from CHD, nonfatal non-procedure-related myocardial infarction, resuscitated cardiac arrest, or fatal or nonfatal stroke). **RESULTS:** In patients 65 years of age or older, absolute risk was reduced by 2.3% and relative risk by 19% for major cardiovascular events in favor of the high-dose atorvastatin group (hazard ratio, 0.81 [95% CI, 0.67 to 0.98]; $P = 0.032$). Among the components of the composite outcome, the mortality rates from CHD, nonfatal non-procedure-related myocardial infarction, and fatal or nonfatal stroke (ischemic, embolic, hemorrhagic, or unknown origin) were all lower in older patients who received high-dose atorvastatin, although the difference was not statistically

significant for each individual component. The improved clinical outcome in patients 65 years of age or older was not associated with persistent elevations in creatine kinase levels.

LIMITATION: Because the study was a secondary analysis, the findings should be interpreted within the context of the main study results. **CONCLUSIONS:** The analysis suggests that additional clinical benefit can be achieved by treating older patients with CHD more aggressively to reduce low-density lipoprotein cholesterol levels to less than 2.6 mmol/L (<100 mg/dL). The findings support the use of intensive low-density lipoprotein cholesterol-lowering therapy in high-risk older persons with established cardiovascular disease. [Click here for related information on atorvastatin.](#)

Wojnicz, R., K. Wilczek, et al. (2006). "Usefulness of atorvastatin in patients with heart failure due to inflammatory dilated cardiomyopathy and elevated cholesterol levels.[see comment]." *American Journal of Cardiology* **97**(6): 899-904.

This study evaluated the safety, tolerability, and efficacy of statin therapy in patients with heart failure secondary to inflammatory dilated cardiomyopathy and moderately elevated low-density lipoprotein cholesterol levels. Seventy-four patients were randomized to receive atorvastatin 40 mg/day or conventional treatment for heart failure. After 6 months of therapy, the predefined primary efficacy end point (an increase of >5% in the absolute left ventricular ejection fraction and > or =2 selected criteria by echocardiography and a decrease in New York Heart Association functional class) was significant in the statin-treated patients ($p = 0.004$). Among secondary efficacy parameters, the quality-of-life index showed a trend suggesting the benefit of statin therapy ($p = 0.055$). In conclusion, the results of this study demonstrate that treatment with atorvastatin in addition to standard therapy for heart failure may significantly improve clinical outcomes in this cohort of patients.