

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

Update #4: Preliminary Scan Report #3

November 2008

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Oregon Evidence-based Practice Center  
Oregon Health & Science University  
Mark Helfand, MD, MPH, Director  
Marian S McDonagh, Principal Investigator,  
Drug Effectiveness Review Project

Update Scan conducted by Susan Carson, MPH



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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)

### Dates of last Preliminary Update Scans

November 2006 (Update 4 Scan #1)

November 2007 (Update 4 Scan #2)

### 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  $\geq 18$  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  $\geq 250$ 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

Table 1. Included drugs

Active ingredient	Brand name
Atorvastatin	Lipitor
Fluvastatin	Lescol
Fluvastatin extended release	Lescol XL
Lovastatin	Mevacor
Lovastatin extended release	Altoprev
Pravastatin	Pravachol
Rosuvastatin	Crestor
Simvastatin	Zocor

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 November 2007 through November Week 3 2008 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/index-eng.php>) websites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote X1) 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 267 citations. Of those, there are 31 potentially relevant new trials (see Appendix A for abstracts). Six new head-to-head trials reported lipid outcomes; 5 of the 6 compared atorvastatin to rosuvastatin (Table 1).

Table 1. Head-to-head trials measuring lipids

Study, year	Comparison	Population
Betteridge 2007a	Atorvastatin vs rosuvastatin	Type 2 diabetes and dyslipidemia
Betteridge 2007b	Atorvastatin vs rosuvastatin	Type 2 diabetes
Insull 2007	Atorvastatin vs rosuvastatin vs simvastatin	High risk for CHD
Leiter 2007	Atorvastatin vs rosuvastatin	High risk for CHD
Sakamoto 2007	Atorvastatin, fluvastatin, or simvastatin vs pravastatin (lipophilic vs hydrophilic statins)	Post MI
Zhu 2007	Atorvastatin vs rosuvastatin	High risk, Asian

Twenty-five publications reported health outcomes. Of these, 17 were post-hoc subgroup analyses or secondary analyses of trials already included in the DERP statins report: There were new publications from ALLHAT, ASCOT-LLA, CARDS, GISSI-P, MIRACL, PROVE-IT, AND TNT. The characteristics of the remaining trials are shown in Table 2.

Table 2. New trials reporting health outcomes

Study	Trial Name	Primary outcome	Comparison	Population
Amerenco 2007	SPARCL	Stroke and major coronary events; subgroup analysis in patients achieving >50% reduction in LDL-c	Atorvastatin vs placebo	Recent stroke or TIA;
Fassett 2008	LORD	Progression of kidney disease	Atorvastatin vs placebo	Chronic kidney disease
Goldstein 2008a	SPARCL	Stroke and CV events; men vs women	Atorvastatin vs placebo	Recent stroke or TIA
Goldstein 2008b	SPARCL	Hemorrhagic stroke	Atorvastatin vs placebo	Recent stroke or TIA
Kjekshus 2007	--	CV death, nonfatal MI, or nonfatal stroke	Rosuvastatin vs placebo	Older patients with systolic heart failure
Mizuno 2008	MEGA	Primary prevention of CV events	Pravastatin + diet vs diet alone	Women
Sato 2008	OACIS-LIPID	Death, nonfatal MI, unstable angina, stroke, revascularization, or rehospitalization for other CV	Rosuvastatin vs placebo	Acute MI

Study	Trial Name	Primary outcome	Comparison	Population
		disease		
Vrotec 2008	--	Sudden cardiac death	Atorvastatin vs no statin	Advanced heart failure

Together with citations identified in Update 4 Scans #1 (N=17) and #2 (N=20) for Update #4, there are now a total of 68 potentially relevant trials for this topic.

### New Drugs

No new drugs were identified.

### New Indications

No new indications were identified

### New Safety Alerts

[Posted 08/08/2008] Simvastatin used with the antiarrhythmic agent amiodarone: FDA notified healthcare professionals of the risk of muscle injury, rhabdomyolysis, which can lead to kidney failure or death, when simvastatin is used with amiodarone. This risk is dose-related and increases when a dose of simvastatin greater than 20 mg per day is given with amiodarone. Although a revision of the simvastatin labeling in 2002 described an increased risk of rhabdomyolysis when amiodarone is taken with simvastatin doses greater than 20 mg daily, FDA continues to receive reports of rhabdomyolysis in patients treated concurrently with amiodarone and simvastatin. Prescribers should be aware of the increased risk of rhabdomyolysis when simvastatin is prescribed with amiodarone, and they should avoid doses of simvastatin greater than 20 mg per day in patients taking amiodarone.

## Appendix A. Abstracts of potentially relevant new trials of statins (N=31)

Amarenco, P., L. B. Goldstein, et al. (2007). "Effects of intense low-density lipoprotein cholesterol reduction in patients with stroke or transient ischemic attack: the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial." *Stroke* 38(12): 3198-204.

**BACKGROUND AND PURPOSE:** The intention-to-treat analysis of data from the placebo-controlled Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial found 80 mg atorvastatin per day reduced the risk of stroke and major coronary events in patients with recent stroke or transient ischemic attack. This benefit was present despite only a 78% net difference in adherence to randomized treatment over the course of the trial. In this exploratory analysis, our aim was to evaluate the benefit and risks associated with achieving a  $\geq 50\%$  low-density lipoprotein cholesterol (LDL-C) reduction from baseline. **METHODS:** This post hoc analysis was based on 55,045 LDL-C measurements among the 4731 patients enrolled in SPARCL (average, 11.6 measurements per patient) during a mean follow-up of 4.9 years. At each postrandomization LDL-C assessment, percent change in LDL-C from baseline for each patient was classified as no change or increase from baseline (32.7% of measurements),  $< 50\%$  LDL-C reduction (39.4%), or  $\geq 50\%$  reduction (27.9%). **RESULTS:** Compared with no change or an increase in LDL-C, analysis of time-varying LDL-C change showed that patients with  $\geq 50\%$  LDL-C reduction had a 31% reduction in stroke risk (hazard ratio, 0.69, 95% CI, 0.55 to 0.87,  $P=0.0016$ ), a 33% reduction in ischemic stroke ( $P=0.0018$ ), no statistically significant increase in hemorrhagic stroke ( $P=0.8864$ ), and a 37% reduction in major coronary events ( $P=0.0323$ ). There was no increase in the incidence of myalgia or rhabdomyolysis. Persistent liver enzyme elevations were more frequent in the group with  $\geq 50\%$  LDL-C reduction. **CONCLUSIONS:** As compared with having no change or an increase in LDL-C, achieving a  $\geq 50\%$  lowering was associated with a greater reduction in the risk of stroke and major coronary events with no increase in brain hemorrhages.

Betteridge, D. J. and J. M. Gibson (2007a). "Effects of rosuvastatin on lipids, lipoproteins and apolipoproteins in the dyslipidaemia of diabetes." *Diabetic Medicine* 24(5): 541-9.

**AIMS:** To compare the effects of rosuvastatin and atorvastatin 10 and 20 mg on plasma lipid and lipoprotein profiles in patients with Type 2 diabetes mellitus and triglycerides  $< \text{or} = 6.0$  mmol/l. **METHODS:** A double-blind, randomized, multicentre study to assess the effect of rosuvastatin and atorvastatin, at 10 mg/day for 8 weeks followed by 20 mg/day for a further 8 weeks, on low-density lipoprotein cholesterol (LDL-C), together with a range of secondary lipid and lipoprotein end points. **RESULTS:** Rosuvastatin reduced mean LDL-C levels from baseline over 16 weeks by 57.4%, while atorvastatin reduced mean LDL-C levels by 46.0% over the same period. The difference in LDL-C reduction between treatments was statistically significant ( $P < 0.001$ ). Rosuvastatin also produced statistically significantly greater mean reductions from baseline in levels of total cholesterol, non-high-density lipoprotein cholesterol, apolipoprotein B and lipid ratios. More patients achieved European LDL-C ( $< 2.5$  mmol/l) and total cholesterol ( $< 4.5$  mmol/l) goals with rosuvastatin than with atorvastatin. Rosuvastatin was associated with a significantly ( $P < 0.049$ ) greater mean percentage increase in glycated haemoglobin (HbA(1c)) from baseline compared with atorvastatin; however, patients in

both treatment groups maintained good glycaemic control. Both rosuvastatin and atorvastatin were well tolerated. CONCLUSIONS: Greater reductions in LDL-C were achieved with rosuvastatin compared with equal doses of atorvastatin, enabling more patients with Type 2 diabetes to achieve European LDL-C goals.

Betteridge, D. J., J. M. Gibson, et al. (2007b). "Comparison of effectiveness of rosuvastatin versus atorvastatin on the achievement of combined C-reactive protein (<2 mg/L) and low-density lipoprotein cholesterol (< 70 mg/dl) targets in patients with type 2 diabetes mellitus (from the ANDROMEDA study)." American Journal of Cardiology 100(8): 1245-8.

Decreasing C-reactive protein (CRP) in addition to decreasing low-density lipoprotein (LDL) cholesterol may further decrease coronary heart disease risk. The effects of rosuvastatin compared with atorvastatin in achieving a combined target of LDL cholesterol <70 mg/dl and CRP <2 mg/L in 509 patients with type 2 diabetes mellitus was evaluated. CRP decreased significantly versus baseline in both treatment groups. Significantly more patients treated with rosuvastatin achieved the combined end point of LDL cholesterol <70 mg/dl and CRP <2 mg/L compared with atorvastatin by the end of the study period (58% vs 37%;  $p < 0.001$  vs atorvastatin). In conclusion, CRP was effectively decreased in patients with type 2 diabetes receiving rosuvastatin or atorvastatin, whereas rosuvastatin decreased LDL cholesterol significantly more than atorvastatin.

Brilakis, E. S., J. A. de Lemos, et al. (2008). "Outcomes of patients with acute coronary syndrome and previous coronary artery bypass grafting (from the Pravastatin or Atorvastatin Evaluation and Infection Therapy [PROVE IT-TIMI 22] and the Aggrastat to Zocor [A to Z] trials)." American Journal of Cardiology 102(5): 552-8.

We examined the effects of intensive statin therapy in patients with acute coronary syndromes (ACSs) and previous coronary artery bypass graft surgery (CABG) participating in the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22 (PROVE-IT TIMI 22) and the Aggrastat to Zocor (A to Z) trials. Of the 8,655 patients enrolled in PROVE IT-TIMI 22 or A to Z, 640 (7.4%) had undergone CABG before enrollment. After a median follow-up of 2 years, compared with patients without previous CABG, those with previous CABG had a higher risk of cardiovascular death (6.2% vs 2.8%), myocardial infarction (14.2% vs 6.6%), and readmission for ACS (7.9% vs 4.4%,  $p < 0.001$  for all comparisons) but a lower rate of repeat coronary revascularization (22.7% vs 26.9%,  $p = 0.01$ ). Compared with moderate statin therapy, intensive statin therapy appeared to decrease the composite of cardiovascular death, myocardial infarction, stroke, and readmission for an ACS (A to Z primary end point) to a similar extent in patients with (26.1% vs 21.6%, hazard ratio 0.84,  $p = 0.27$ ) and without (13.9% vs 12.0%, hazard ratio 0.86,  $p = 0.016$ ) previous CABG, although the decrease was not statistically significant in the previous CABG group, likely due to the small number of patients with previous CABG. In conclusion, compared with patients with ACS without previous CABG, those with previous CABG have a higher risk for adverse cardiac events and may derive similar benefit from intensive statin therapy.

Chiodini, B. D., M. G. Franzosi, et al. (2007). "Apolipoprotein E polymorphisms influence effect of pravastatin on survival after myocardial infarction in a Mediterranean population: the GISSI-Prevenzione study." *European Heart Journal* 28(16): 1977-83.

AIMS: Controversy exists with regard to the influence of APOE polymorphisms on coronary heart disease development and on the efficacy of statin treatment. We investigated the relationship between apoe, mortality and the response to treatment in Mediterranean myocardial infarction (mi) survivors. METHODS AND RESULTS: We analysed 3304 Italian patients with MI randomized to pravastatin or no treatment in the GISSI-Prevenzione study, with a mean follow-up time of 23.0 +/- 6.7 months (median 24.3 months). Mortality curves were calculated using Kaplan-Meier method, and differences in survival were tested using the log-rank test. There were 109 deaths during follow-up. Patients treated with pravastatin showed a significant decrease in mortality compared with non-treated patients (HR 0.67, 95% confidence interval 0.45-0.97, P = 0.038). Among the 3304 patients, 554 (16.8%) were epsilon4 carriers and 2750 (83.2%) were non-epsilon4 carriers. No significant difference in terms of mortality was observed between the epsilon4 and the non-epsilon4 carriers (3.61% vs. 3.24%, P = 0.67). However, although in non-epsilon4 carriers no significant difference in mortality was observed between patients treated with pravastatin and non-treated (2.81% vs. 3.67%, P = 0.21), among the epsilon4 carriers a significant reduction in mortality was observed in patients treated compared with non-treated (1.85% vs. 5.28%, P = 0.023). CONCLUSION: We found that epsilon4 allele is a determinant of pravastatin response in terms of survival. Though in the entire population investigated, we found a beneficial effect of pravastatin in terms of survival, only the epsilon4 carriers seemed to have gained a significant benefit from this treatment. We suggest that the effect of statins is of particular interest in this fraction of the population. Genetic markers can help in identifying patients that benefit more from statin treatment.

Fassett, R. G., M. J. Ball, et al. (2008). "The Lipid lowering and Onset of Renal Disease (LORD) Trial: a randomized double blind placebo controlled trial assessing the effect of atorvastatin on the progression of kidney disease." *BMC Nephrology* 9: 4.

BACKGROUND: There is evidence that dyslipidemia is associated with chronic kidney disease (CKD). Experimental studies have established that lipids are damaging to the kidney and animal intervention studies show statins attenuate this damage. Small clinical trials, meta-analyses, observational studies and post-hoc analyses of cardiovascular intervention studies all support the concept that statins can reduce kidney damage in humans. Based on this background, a double blind randomized placebo controlled trial was designed to assess the effectiveness of atorvastatin 10 mg on slowing the progression of kidney disease in a population of patients with CKD. METHOD/DESIGN: The Lipid lowering and Onset of Renal Disease (LORD) trial is a three-year, single center, multi-site, double blind, randomized, placebo controlled trial. The primary outcome measure is kidney function measured by eGFR calculated by both Modification of Diet in Renal Disease (MDRD) and Cockcroft and Gault equations. Secondary outcome measures include kidney function measured by 24-hour urine creatinine clearance and also 24-hour urinary protein excretion, markers of oxidative stress, inflammation and drug safety and tolerability. DISCUSSION: The results of this study will help determine the effectiveness and safety of atorvastatin and establish its effects on oxidative stress and inflammation in patients with CKD. TRIAL REGISTRATION: ANZCTRN012605000693628.

Giraldez, R. R., R. P. Giugliano, et al. (2008). "Baseline low-density lipoprotein cholesterol is an important predictor of the benefit of intensive lipid-lowering therapy: a PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22) analysis.[see comment]." Journal of the American College of Cardiology 52(11): 914-20.

**OBJECTIVES:** This study sought to determine whether the benefit of intensive lipid-lowering therapy (LLT) is dependent on baseline low-density lipoprotein cholesterol (LDL-C). **BACKGROUND:** Aggressive LDL-C reduction with statins improves cardiovascular outcomes in acute and chronic coronary heart disease (CHD). The importance of baseline LDL-C is unclear. **METHODS:** We compared 2-year composites of death, myocardial infarction (MI), unstable angina, revascularization >30 days, and stroke (primary end point), and CHD death, MI, and revascularization >30 days (secondary end point) in 2,986 statin-naive patients with recent acute coronary syndrome (ACS) randomized to atorvastatin 80 mg versus pravastatin 40 mg in the PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22) study stratified by quartiles of baseline LDL-C. Multivariable models assessed whether the treatment benefit was dependent on baseline LDL-C. **RESULTS:** A significant reduction in the hazards of the primary (hazard ratio [HR]: 0.63, 95% confidence interval [CI]: 0.47 to 0.85,  $p = 0.002$ ) and secondary (HR: 0.57, 95% CI: 0.42 to 0.79,  $p = 0.001$ ) end points occurred in patients within the highest quartile (>132 mg/dl) of baseline LDL-C treated with atorvastatin 80 mg. The benefit of intensive therapy progressively declined as baseline LDL-C decreased. The lowest quartile (LDL-C  $\leq 92$  mg/dl) experienced similar rates of the primary (HR: 0.93, 95% CI: 0.69 to 1.25,  $p = 0.63$ ) and secondary (HR: 0.98, 95% CI: 0.71 to 1.35,  $p = 0.89$ ) end points. Adjusted interaction tests between treatment and highest versus lowest baseline LDL-C quartile were significant for the primary and secondary end points ( $p = 0.03$  and  $p = 0.007$ , respectively). Analyzing baseline LDL-C as a continuous variable, atorvastatin 80 mg was associated with improved outcomes provided the baseline LDL-C was >66 mg/dl. **CONCLUSIONS:** A progressive reduction in the benefit of intensive LLT with atorvastatin 80 mg over pravastatin 40 mg occurred in statin-naive ACS patients as baseline LDL-C declined. (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 [PROVE IT-TIMI 22]; NCT00382460).

Goldstein, L. B., P. Amarenco, et al. (2008). "Relative effects of statin therapy on stroke and cardiovascular events in men and women: secondary analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Study." Stroke 39(9): 2444-8.

**BACKGROUND AND PURPOSE:** In SPARCL, treatment with atorvastatin 80 mg daily reduced stroke risk in patients with recent stroke or TIA and no known coronary heart disease by 16% versus placebo over 4.9 years of follow-up. The purpose of this secondary analysis was to determine whether men and women similarly benefited from randomization to statin treatment. **METHODS:** The effect of sex on treatment-related reductions in stroke and other cardiovascular outcomes were analyzed with Cox regression modeling testing for sex by treatment interactions. **RESULTS:** Women ( $n=1908$ ) constituted 40% of the SPARCL study population. At baseline, men ( $n=2823$ ) were younger ( $62.0 \pm 0.21$  versus  $63.9 \pm 0.27$  years), had lower systolic BPs ( $138.1 \pm$

0.35 versus 139.5 $\pm$ 0.47 mm Hg), higher diastolic BPs (82.2 $\pm$ 0.20 versus 81.0 $\pm$ 0.25 mm Hg), more frequently had a history of smoking (73% versus 38%), and had lower total cholesterol (207.0 $\pm$ 0.54 versus 218.9 $\pm$ 0.67 mg/dL) and LDL-C levels (132 $\pm$ 0.45 versus 134 $\pm$ 0.57 mg/dL) than women. Use of antithrombotics and antihypertensives were similar. After prespecified adjustment for region, entry event, time since event, and age, there were no sex by treatment interactions for the combined risk of nonfatal and fatal stroke (treatment Hazard Ratio, HR=0.84, 95% CI 0.68, 1.02 in men versus HR=0.84, 95% CI 0.63, 1.11 in women; treatment x sex interaction P=0.99), major cardiac events (HR=0.61, 95% CI 0.42, 0.87 in men versus HR=0.76, 95% CI 0.48, 1.21 in women; P=0.45), major cardiovascular events (HR=0.78, 95% CI 0.65, 0.93 in men versus HR=0.84, 95% CI 0.65, 1.07 in women; P=0.63), revascularization procedures (HR=0.50, 95% CI 0.37, 0.67 in men versus HR=0.76, 95% CI 0.46, 1.24 in women; P=0.17), or any CHD event (HR=0.54, 95% CI 0.41, 0.72 in men versus 0.67 95% CI 0.46, 0.98 in women; P=0.40). CONCLUSIONS: Stroke and other cardiovascular events are similarly reduced with atorvastatin 80 mg/d in men and women with recent stroke or TIA.

Goldstein, L. B., P. Amarenco, et al. (2008). "Hemorrhagic stroke in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels study.[see comment]." *Neurology* 70(24 Pt 2): 2364-70.

**BACKGROUND:** In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study, atorvastatin 80 mg/day reduced the risk of stroke in patients with recent stroke or TIA. Post hoc analysis found this overall benefit included an increase in the numbers of treated patients having hemorrhagic stroke (n = 55 for active treatment vs n = 33 for placebo). **METHODS:** We explored the relationships between hemorrhage risk and treatment, baseline patient characteristics, most recent blood pressure, and most recent low-density lipoprotein (LDL) cholesterol levels prior to the hemorrhage. **RESULTS:** Of 4,731 patients, 67% had ischemic strokes, 31% TIAs, and 2% hemorrhagic strokes as entry events. In addition to atorvastatin treatment (HR 1.68, 95% CI 1.09 to 2.59, p = 0.02), Cox multivariable regression including baseline variables significant in univariable analyses showed that hemorrhagic stroke risk was higher in those having a hemorrhagic stroke as the entry event (HR 5.65, 95% CI 2.82 to 11.30, p < 0.001), in men (HR 1.79, 95% CI 1.13 to 2.84, p = 0.01), and with age (10 y increments, HR 1.42, 95% CI 1.16 to 1.74, p = 0.001). There were no statistical interactions between these factors and treatment. Multivariable analyses also found that having Stage 2 (JNC-7) hypertension at the last study visit before a hemorrhagic stroke increased risk (HR 6.19, 95% CI 1.47 to 26.11, p = 0.01), but there was no effect of most recent LDL-cholesterol level in those treated with atorvastatin. **CONCLUSIONS:** Hemorrhagic stroke was more frequent in those treated with atorvastatin, in those with a hemorrhagic stroke as an entry event, in men, and increased with age. Those with Stage 2 hypertension at the last visit prior to the hemorrhagic stroke were also at increased risk. Treatment did not disproportionately affect the hemorrhagic stroke risk associated with these other factors. There were no relationships between hemorrhage risk and baseline low-density lipoprotein (LDL) cholesterol level or recent LDL cholesterol level in treated patients.

Hitman, G. A., H. Colhoun, et al. (2007). "Stroke prediction and stroke prevention with atorvastatin in the Collaborative Atorvastatin Diabetes Study (CARDS).[see comment]." Diabetic Medicine 24(12): 1313-21.

AIMS: Patients with Type 2 diabetes have an elevated risk of stroke. The role of lipid levels and diabetes-specific factors in risk prediction of stroke is unclear, and estimates of efficacy of lipid-lowering therapy vary between trials. We examined predictors of stroke and the effect of atorvastatin on specific stroke subtypes in Type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS) [a trial of 2838 participants with mean low-density lipoprotein cholesterol < 4.14 mmol/l, no history of macrovascular disease and randomized to atorvastatin 10 mg daily or placebo]. METHODS: Median follow-up was 3.9 years. Cox regression models were used to estimate the effect of atorvastatin on stroke rate and risk of stroke associated with baseline risk factors. Risk factors that predicted stroke in univariate models were examined in a multivariable model. RESULTS: Independent risk factors predicting stroke were age [10-year increments; hazard ratio (HR) 2.3, P < 0.001], microalbuminuria (albumin : creatinine ratio > 2.5 mg/mmol; HR 2.0, P = 0.007) and glycaemic control (HbA(1c) > 10%; HR 2.7, P = 0.007). Women were at lower risk of stroke (HR 0.3, P = 0.004). Lipids did not predict stroke. Of 60 first strokes, 47 were non-haemorrhagic, 13 were indeterminate and none was definitely haemorrhagic. Atorvastatin treatment was associated with 50% reduction in non-haemorrhagic stroke (95% confidence interval 9%-72%P = 0.024), similar to the 48% reduction (11%-69%) for all strokes combined. CONCLUSIONS: Diabetes-specific risk factors are important predictors of stroke in Type 2 diabetes. Despite the lack of association between baseline lipids and first stroke, there was a reduction of 50% of non-haemorrhagic strokes associated with atorvastatin treatment in the CARDS population.

Iakoubova, O. A., M. S. Sabatine, et al. (2008). "Polymorphism in KIF6 gene and benefit from statins after acute coronary syndromes: results from the PROVE IT-TIMI 22 study.[see comment]." Journal of the American College of Cardiology 51(4): 449-55.

OBJECTIVES: We explored whether the benefit of intensive versus moderate statin therapy would be greater in carriers of KIF6 719Arg than in noncarriers. BACKGROUND: The 719Arg variant of Trp719Arg (rs20455), a polymorphism in kinesin-like protein 6, is associated with greater risk of coronary events and greater benefit from pravastatin versus placebo. METHODS: We genotyped 1,778 acute coronary syndrome patients within the PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy: Thrombolysis in Myocardial Infarction 22) trial and investigated different intensities of statin therapy in carriers of 719Arg and in noncarriers using Cox proportional hazards models that adjusted for traditional risk factors. RESULTS: Benefit from intensive, compared with moderate, statin therapy was significantly greater in the 59% of the cohort who were carriers (hazard ratio [HR] 0.59, 95% confidence interval [CI] 0.45 to 0.77) than in those who were noncarriers (HR 0.94, 95% CI 0.70 to 1.27; p = 0.018 for interaction between 719Arg carrier status and treatment). Absolute risk reduction was 10.0% in carriers versus 0.8% in noncarriers. The benefit of intensive therapy in carriers was significant as early as day 30 of therapy. Carriers and noncarriers did not differ in on-treatment low-density lipoprotein cholesterol, triglyceride, or C-reactive protein (CRP) levels. CONCLUSIONS: Carriers of 719Arg receive significantly greater benefit from intensive statin therapy than do

noncarriers, a superior benefit that appears to be due to a mechanism distinct from lipid or CRP lowering. Functional studies of the KIF6 kinesin are warranted, given the consistent association of Trp719Arg with risk of coronary events and statin benefit.

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][erratum appears in Mayo Clin Proc. 2007 Jul;82(7):890]." 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.

Kinlay, S., G. G. Schwartz, et al. (2008). "Inflammation, statin therapy, and risk of stroke after an acute coronary syndrome in the MIRACL study." Arteriosclerosis, Thrombosis & Vascular Biology 28(1): 142-7.

**OBJECTIVE:** Patients with acute coronary syndromes have an increased risk of stroke. We measured markers of inflammation in the MIRACL study, a randomized trial of atorvastatin versus placebo in acute coronary syndromes, to assess the relationship of inflammation to stroke. **METHODS AND RESULTS:** Baseline C-reactive protein (CRP), serum amyloid A (SAA), and interleukin-6 (IL-6) were collected in 2926 (95%) subjects. Baseline markers were related to stroke risk over the 16 weeks of the study. Subjects who subsequently experienced a stroke had higher CRP (27.5 versus 10.2 mg/L,  $P=0.0032$ ), SAA (30.5 versus 16.0 mg/L,  $P=0.031$ ), IL-6 (11 231 versus 6841 pg/L,  $P=0.004$ ), and troponin (6.03 versus 3.19 ng/mL  $P=0.0032$ ). The risk of stroke was related to greater CRP, SAA, and IL-6 in the placebo group only. Similarly, there was a graded increase in

risk of stroke across quartiles of inflammatory markers in the placebo patients only.  
CONCLUSIONS: In acute coronary syndromes, the early risk of stroke relates to both heightened inflammation and size of myocardial necrosis. Treatment with atorvastatin abrogated the risk associated with elevated markers of inflammation in this study, a finding that provides a novel rationale for the use of statins in acute coronary syndromes.

Kjekshus, J., E. Apetrei, et al. (2007). "Rosuvastatin in older patients with systolic heart failure.[see comment]." *New England Journal of Medicine* 357(22): 2248-61.

BACKGROUND: Patients with systolic heart failure have generally been excluded from statin trials. Acute coronary events are uncommon in this population, and statins have theoretical risks in these patients. METHODS: A total of 5011 patients at least 60 years of age with New York Heart Association class II, III, or IV ischemic, systolic heart failure were randomly assigned to receive 10 mg of rosuvastatin or placebo per day. The primary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Secondary outcomes included death from any cause, any coronary event, death from cardiovascular causes, and the number of hospitalizations. RESULTS: As compared with the placebo group, patients in the rosuvastatin group had decreased levels of low-density lipoprotein cholesterol (difference between groups, 45.0%;  $P < 0.001$ ) and of high-sensitivity C-reactive protein (difference between groups, 37.1%;  $P < 0.001$ ). During a median follow-up of 32.8 months, the primary outcome occurred in 692 patients in the rosuvastatin group and 732 in the placebo group (hazard ratio, 0.92; 95% confidence interval [CI], 0.83 to 1.02;  $P = 0.12$ ), and 728 patients and 759 patients, respectively, died (hazard ratio, 0.95; 95% CI, 0.86 to 1.05;  $P = 0.31$ ). There were no significant differences between the two groups in the coronary outcome or death from cardiovascular causes. In a prespecified secondary analysis, there were fewer hospitalizations for cardiovascular causes in the rosuvastatin group (2193) than in the placebo group (2564) ( $P < 0.001$ ). No excessive episodes of muscle-related or other adverse events occurred in the rosuvastatin group. CONCLUSIONS: Rosuvastatin did not reduce the primary outcome or the number of deaths from any cause in older patients with systolic heart failure, although the drug did reduce the number of cardiovascular hospitalizations. The drug did not cause safety problems. (ClinicalTrials.gov number, NCT00206310.) 2007 Massachusetts Medical Society

Kostis, J. B., A. Breazna, et al. (2008). "The benefits of intensive lipid lowering in patients with stable coronary heart disease with normal or high systolic blood pressure: an analysis of the Treating to New Targets (TNT) study." *Journal of Clinical Hypertension* 10(5): 367-76.

This post-hoc analysis of the Treating to New Targets (TNT) study evaluated the joint effects of managing low-density lipoprotein cholesterol (LDL-C) and systolic blood pressure (SBP) on cardiovascular outcomes. Patients (N=9739) with clinically evident, stable coronary heart disease (CHD) were randomized to atorvastatin 10 or 80 mg/d. The primary end point was occurrence of a first major cardiovascular event. At 3 months' follow-up, patients were stratified according to SBP ( $< 140$  mm Hg vs  $\geq 140$  mm Hg) and tertiles of LDL-C. At 4.9 years' median follow-up, the rate of major cardiovascular events was reduced most in patients with lower LDL-C ( $P < .001$ ) and in patients with SBP  $< 140$  mm Hg ( $P = .014$ ). A 42% relative risk reduction was observed for patients in the lowest LDL-C tertile with an SBP  $< 140$  mm Hg, compared with

patients in the highest LDL-C tertile with an SBP  $\geq$  140 mm Hg. The effect of lower SBP on stroke was most pronounced in the lowest LDL-C tertile.

Leiter, L. A., R. S. Rosenson, et al. (2007). "Efficacy and safety of rosuvastatin 40 mg versus atorvastatin 80 mg in high-risk patients with hypercholesterolemia: results of the POLARIS study." *Atherosclerosis* 194(2): e154-64.

POLARIS investigated the efficacy and safety of rosuvastatin 40 mg and atorvastatin 80 mg in high-risk patients with hypercholesterolemia. Patients (n=871) were randomized to rosuvastatin 40 mg/day or atorvastatin 80 mg/day for 26 weeks. The primary endpoint was percentage change in LDL-C levels at 8 weeks. Secondary assessments included safety and tolerability, NCEP ATP III LDL-C goal achievement, change in other lipids and lipoproteins at 8 and 26 weeks, and health economics. Mean LDL-C levels were reduced significantly more with rosuvastatin 40 mg than with atorvastatin 80 mg at 8 weeks (-56% versus -52%,  $p < 0.001$ ). The proportion of patients achieving the NCEP ATP III LDL-C goal at 8 weeks was significantly higher in the rosuvastatin 40 mg group (80% versus 72%,  $p < 0.01$ ). Significant differences in the change from baseline in high-density lipoprotein cholesterol (HDL-C) (+9.6% versus +4.4%) and apolipoprotein (Apo)A-I levels (+4.2 versus -0.5) were observed between rosuvastatin and atorvastatin (all  $p < 0.05$ ). Both treatments were well tolerated. Based on a US analysis, rosuvastatin used fewer resources and delivered greater efficacy. Intensive lipid-lowering therapy with rosuvastatin 40 mg/day provided greater LDL-C-lowering efficacy than atorvastatin 80 mg/day, enabling more patients to achieve LDL-C goals. Rosuvastatin may therefore improve LDL-C goal achievement in high-risk patients with hypercholesterolemia.

Lotfi, A., M. J. Schweiger, et al. (2008). "High-dose atorvastatin does not negatively influence clinical outcomes among clopidogrel treated acute coronary syndrome patients--a Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) analysis." *American Heart Journal* 155(5): 954-8.

**BACKGROUND:** Clopidogrel is inactive in vitro and is metabolized by hepatic cytochrome P-450-3A4 to produce active metabolites. Unlike pravastatin, atorvastatin is a statin that is subject to metabolism by cytochrome P-450-3A4, and drug-drug interactions with other potent inhibitors of this cytochrome system have been demonstrated. However, the clinical impact of this interaction has created debate.

**METHODS:** In the PROVE IT-TIMI 22 study, 4162 patients with an acute coronary syndrome within the preceding 10 days were randomly assigned in a 1:1 fashion to pravastatin 40 mg or atorvastatin 80 mg daily. The primary efficacy outcome measure was the time from randomization until the first occurrence of a component of the primary end point: death from any cause, myocardial infarction, documented unstable angina requiring rehospitalization, revascularization with either percutaneous coronary intervention or coronary artery bypass grafting, or stroke.

**RESULTS:** At 30 days, there was a trend for less occurrence of the primary end point in patients randomized to atorvastatin compared with pravastatin, irrespective of whether they were taking clopidogrel. This becomes significant at 2-year follow-up in clopidogrel-treated patients (21.66% vs 26.18%  $P = .0091$ ). There was no evidence of interaction in the clopidogrel/no clopidogrel subgroup for the primary end point (interaction  $P = .65$ ) or the components of the composite.

**CONCLUSION:** In conclusion, the beneficial affects of

atorvastatin 80 mg in reducing the primary end point at 2 years is independent of coadministration with clopidogrel.

McLean, D. S., S. Ravid, et al. (2008). "Effect of statin dose on incidence of atrial fibrillation: data from the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) and Aggrastat to Zocor (A to Z) trials." American Heart Journal 155(2): 298-302.

**BACKGROUND:** Inflammation has been suggested as a factor in the initiation and maintenance of atrial fibrillation (AF). Several observational studies have suggested that statins, presumably through their anti-inflammatory properties, decrease the risk of AF. **METHODS:** We analyzed 2 large, randomized trials, PROVE IT-TIMI 22 and phase Z of the A to Z trial, which compared lower- versus higher-intensity statin therapy to evaluate whether higher-intensity statin therapy lowered the risk of AF onset during the 2 years of follow-up. We hypothesized that higher-intensity statin therapy would decrease the risk of AF when compared to lower-intensity statin therapy. From each trial, patients experiencing the onset of AF during follow-up were identified from the adverse event reports. **RESULTS:** Neither study showed a decreased AF risk with higher-dose statin. In PROVE IT-TIMI 22, 2.9% versus 3.3% in the high- versus standard-dose statin therapy, respectively, experienced the onset of AF over 2 years (OR 0.86, 95% CI 0.61-1.23, P = .41). In A to Z, rates were 1.6% versus 0.99%, respectively (OR 1.58, 95% CI 0.92-2.70, P = .096). In both trials, C-reactive protein levels (plasma or serum) tended to be higher among patients experiencing the onset of AF. **CONCLUSION:** Our randomized comparison among 8659 patients found that higher-dose statin therapy did not reduce the short term incidence of AF among patients after acute coronary syndromes when compared with standard dose statin treatment.

Mizuno, K., N. Nakaya, et al. (2008). "Usefulness of pravastatin in primary prevention of cardiovascular events in women: analysis of the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA study)." Circulation 117(4): 494-502.

**BACKGROUND:** It is well known that statins reduce the risk of cardiovascular disease. However, the effect of statins in women for the primary prevention of cardiovascular disease has not been determined. We conducted an exploratory analysis of the effect of diet plus pravastatin therapy on the primary prevention of cardiovascular events in women with data from a large-scale primary prevention trial with pravastatin. **METHODS AND RESULTS:** Patients with hypercholesterolemia (5.7 to 7.0 mmol/L) and no history of coronary heart disease or stroke were randomized to diet or diet plus pravastatin 10 to 20 mg/d and followed up for > or = 5 years. We investigated the effect of diet plus pravastatin treatment on cardiovascular events in 5356 women during the 5-year follow-up. The incidence of cardiovascular events in the women was 2 to 3 times lower than that in men. The occurrence of cardiovascular events was 26% to 37% lower in the diet plus pravastatin treatment group than in the diet alone group. Although these differences did not reach statistical significance, the overall risk reductions were similar to those in men. Notably, women > or = 60 years of age treated with diet plus pravastatin had markedly higher risk reductions for coronary heart disease (45%), coronary heart disease plus cerebral infarction (50%), and stroke (64%) than did women treated with diet alone. **CONCLUSIONS:** Treatment with pravastatin in women with elevated cholesterol but no history of cardiovascular disease provides a benefit similar to that seen in men,

and this benefit is more marked in older women. This treatment should be considered routinely for primary cardiovascular protection in women with elevated cholesterol levels.

Newman, C. B., M. Szarek, et al. (2008). "The safety and tolerability of atorvastatin 10 mg in the Collaborative Atorvastatin Diabetes Study (CARDS)." Diabetes & Vascular Disease Research 5(3): 177-83.

The objective of this study was to evaluate the safety and tolerability of atorvastatin 10 mg compared with placebo in 2,838 patients with type 2 diabetes and no history of coronary heart disease who were enrolled in the Collaborative Atorvastatin Diabetes Study (CARDS) and followed for 3.9 years. The percentages of patients experiencing treatment-associated adverse events (AEs), serious AEs and discontinuations due to AEs in the atorvastatin (n=1,428) and placebo (n=1,410) groups were 23.0% vs. 25.4%, 1.1% vs. 1.1% and 2.9% vs. 3.4%, respectively. The most common treatment-associated AEs in the atorvastatin and placebo groups were digestive system-related (8.9% vs. 10.0%). All-cause and treatment-associated myalgia were reported in 4.0% and 1.0% of atorvastatin-treated patients, and 4.8% and 1.2% of placebo-treated patients. An analysis of selected AEs by tertiles of baseline low-density lipoprotein (LDL) cholesterol showed no relationship between LDL cholesterol levels and the incidence of myalgia, cancer or nervous system AEs in either treatment group. Overall, these data demonstrate that atorvastatin 10 mg was well tolerated in patients with type 2 diabetes during long-term treatment.

Rahman, M., C. Baimbridge, et al. (2008). "Progression of kidney disease in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin versus usual care: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).[see comment]." American Journal of Kidney Diseases 52(3): 412-24.

BACKGROUND: Dyslipidemia is common in patients with chronic kidney disease. The role of statin therapy in the progression of kidney disease is unclear. STUDY DESIGN: Prospective randomized clinical trial, post hoc analyses. SETTING & PARTICIPANTS: 10,060 participants in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (lipid-lowering component) stratified by baseline estimated glomerular filtration rate (eGFR): less than 60, 60 to 89, and 90 or greater mL/min/1.73 m<sup>2</sup>. Mean follow-up was 4.8 years. INTERVENTION: Randomized; pravastatin, 40 mg/d, or usual care. OUTCOMES & MEASUREMENTS: Total, high-density lipoprotein, and low-density lipoprotein cholesterol; end-stage renal disease (ESRD), eGFR. RESULTS: Through year 6, total cholesterol levels decreased in the pravastatin (-20.7%) and usual-care groups (-11.2%). No significant differences were seen between groups for rates of ESRD (1.36 v 1.45/100 patient-years; P = 0.9), composite end points of ESRD and 50% or 25% decrease in eGFR, or rate of change in eGFR. Findings were consistent across eGFR strata. In patients with eGFR of 90 mL/min/1.73 m<sup>2</sup> or greater, the pravastatin arm tended to have a higher eGFR. LIMITATIONS: Proteinuria data unavailable, post hoc analyses, unconfirmed validity of the Modification of Diet in Renal Disease Study equation in normal eGFR range, statin drop-in rate in usual-care group with small cholesterol differential between groups. CONCLUSIONS: In hypertensive patients with moderate dyslipidemia and decreased eGFR, pravastatin was not superior to usual care in preventing clinical renal outcomes. This was consistent across the strata of baseline

eGFR. However, benefit from statin therapy may depend on the degree of the cholesterol level decrease achieved.

Sakamoto, T., S. Kojima, et al. (2007). "Usefulness of hydrophilic vs lipophilic statins after acute myocardial infarction: subanalysis of MUSASHI-AMI." Circulation Journal 71(9): 1348-53.

BACKGROUND: Statins are widely used to reduce blood levels of low-density lipoprotein-cholesterol (LDL-C). Each statin has unique pharmacokinetic properties; lipophilicity is one such property and relates to tissue selectivity. METHODS AND RESULTS: The Multicenter Study for Aggressive Lipid-lowering Strategy by HMG-CoA Reductase Inhibitors in Patients with Acute Myocardial Infarction (MUSASHI-AMI) trial evaluated the effect of discretionary statin treatment initiated within 96 h after onset of acute myocardial infarction (AMI) in Japanese patients. To clarify whether statin lipophilicity affects prognosis, a post hoc analysis of the MUSASHI-AMI database was performed. Patients who were assigned to receive statin were separated into 2 groups according to the lipophilicity of the statins they were administered: lipophilic statins (atorvastatin, fluvastatin, pitavastatin and simvastatin; LS group; n=131) or hydrophilic statins (pravastatin; HS group; n=110). There was no difference in baseline LDL-C concentrations between the 2 groups. Although LDL-C was decreased more potently in the LS than HS groups (-34% vs -19%; p=0.0069), acute coronary syndrome events tended to occur less frequently (3.6% vs 9.9%; p=0.0530) and the incidence of new Q-wave appearance in electrocardiogram was significantly lower (75% vs 89%; p=0.0056) in the HS than LS groups. CONCLUSIONS: In normocholesterolemic Japanese patients after AMI, hydrophilic pravastatin could be superior to lipophilic statins at preventing new Q-wave appearance and reducing cardiovascular events.

Sato, H., K. Kinjo, et al. (2008). "Effect of early use of low-dose pravastatin on major adverse cardiac events in patients with acute myocardial infarction: the OACIS-LIPID Study." Circulation Journal 72(1): 17-22.

BACKGROUND: It is unclear whether early initiation of low-dose pravastatin therapy can reduce the occurrence of major adverse cardiac events after acute myocardial infarction (AMI). METHODS AND RESULTS: The study group comprised 353 patients with AMI who had plasma total cholesterol levels of 200-250 mg/dl and triglyceride levels <300 mg/dl. The patients were randomly assigned to either receive pravastatin (10 mg/daily, n=176) or not (n=177). The primary endpoint was a composite of death, nonfatal myocardial infarction (MI), unstable angina (UA), stroke, revascularization, and rehospitalization because of other cardiovascular disease. The follow-up period was 9 months. The primary endpoint occurred in 31 patients (17.9%) in the pravastatin group and 55 patients (31.4%) in the non-pravastatin group (relative risk, 0.56; 95% confidence interval, 0.36-0.87). There were no significant differences in the risk of death, nonfatal MI, UA, and stroke between the 2 groups, although the pravastatin group had a lower risk of need for revascularization. CONCLUSION: For patients with AMI, early and low-dose pravastatin therapy (10 mg/daily) reduces recurrent major adverse cardiac events, mostly the requirement for revascularization.

Sever, P. S., N. R. Poulter, et al. (2008). "The Anglo-Scandinavian Cardiac Outcomes Trial lipid lowering arm: extended observations 2 years after trial closure.[see comment]." European Heart Journal 29(4): 499-508.

**AIMS:** To determine the cardiovascular benefits in those originally assigned atorvastatin in the Anglo-Scandinavian Cardiac Outcomes Trial-2.2 years after closure of the lipid-lowering arm of the trial (ASCOT-LLA). **METHODS AND RESULTS:** The Blood Pressure Lowering Arm of the ASCOT trial (ASCOT-BPLA) compared two different antihypertensive treatment strategies on cardiovascular outcomes. ASCOT-LLA was a double-blind placebo-controlled trial of atorvastatin in those enrolled into ASCOT-BPLA with total cholesterol concentrations at baseline of  $<$  or  $=6.5$  mmol/L. A total of 19 342 hypertensive patients were enrolled in ASCOT-BPLA and 10 305 were further assigned either atorvastatin, 10 mg, or placebo. ASCOT-LLA was stopped prematurely after a median 3.3 years follow-up because of substantial cardiovascular benefits in those assigned atorvastatin. Trial physicians were invited to offer atorvastatin to all ASCOT-LLA patients until the end of ASCOT-BPLA. The primary outcome of ASCOT-LLA was combined fatal coronary heart disease (CHD) or non-fatal myocardial infarction. Secondary outcomes included all coronary events, all cardiovascular events and procedures, fatal and non-fatal stroke, cardiovascular mortality, all cause mortality, development of chronic stable angina, heart failure, and peripheral arterial disease. By the end of ASCOT-LLA, there was a 36% relative risk reduction in primary events ( $n = 254$ ) in favour of atorvastatin [hazard ratio (HR) 0.64, 95% CI: 0.50-0.83,  $P = 0.0005$ ]. At the end of ASCOT-BPLA, 2.2 years later, despite extensive crossovers from and to statin usage, the relative risk reduction in primary events ( $n = 412$ ) among those originally assigned atorvastatin remained at 36% (HR 0.64, 95% CI: 0.53-0.78,  $P = 0.0001$ ). For almost all other endpoints, risk reductions also remained essentially unchanged and in the case of all cause mortality, the risk reduction of 15% now achieved borderline statistical significance ( $P = 0.02$ ). **CONCLUSION:** Carry-over benefits from those originally assigned atorvastatin but no longer taking the drug may account for unchanged relative risk reductions in most cardiovascular endpoints observed 2 years after ASCOT-LLA closed.

Shah, S. J., D. D. Waters, et al. (2008). "Intensive lipid-lowering with atorvastatin for secondary prevention in patients after coronary artery bypass surgery." Journal of the American College of Cardiology 51(20): 1938-43.

**OBJECTIVES:** The aim of this post hoc analysis from the TNT (Treating to New Targets) trial is to determine whether patients with previous coronary artery bypass grafting (CABG) surgery achieved clinical benefit from intensive low-density lipoprotein (LDL)-cholesterol lowering. **BACKGROUND:** The development and progression of atherosclerosis is accelerated in coronary venous bypass grafts. **METHODS:** A total of 10,001 patients with documented coronary disease, including 4,654 with previous CABG, were randomized to atorvastatin 80 or 10 mg/day and were followed for a median of 4.9 years. The primary end point was the occurrence of a first major cardiovascular event (cardiac death, nonfatal myocardial infarction, resuscitated cardiac arrest, or stroke). **RESULTS:** A first major cardiovascular event occurred in 11.4% of the patients with prior CABG and 8.5% of those without prior CABG ( $p < 0.001$ ). In CABG patients, mean LDL-cholesterol levels at study end were 79 mg/dl in the 80-mg arm and 101 mg/dl in the 10-mg arm, and the primary event rate was 9.7% in the 80-mg arm and 13.0% in the 10-mg arm (hazard ratio 0.73, 95% confidence interval 0.62 to 0.87,  $p = 0.0004$ ). Repeat revascularization during follow-up, either CABG or percutaneous coronary intervention, was performed in 11.3% of the CABG patients in the 80-mg arm and 15.9%

in the 10-mg arm (hazard ratio 0.70, 95% confidence interval 0.60 to 0.82,  $p < 0.0001$ ).  
**CONCLUSIONS:** Intensive LDL-cholesterol lowering to a mean of 79 mg/dl with atorvastatin 80 mg/day in patients with previous CABG reduces major cardiovascular events by 27% and the need for repeat coronary revascularization by 30%, compared with less intensive cholesterol-lowering to a mean of 101 mg/dl with atorvastatin 10 mg/day. (A Study to Determine the Degree of Additional Reduction in CV Risk in Lowering LDL Below Minimum Target Levels [TNT]; NCT00327691).

Shepherd, J., J. J. Kastelein, et al. (2008). "Intensive lipid lowering with atorvastatin in patients with coronary heart disease and chronic kidney disease: the TNT (Treating to New Targets) study." *Journal of the American College of Cardiology* 51(15): 1448-54.

**OBJECTIVES:** This subanalysis of the TNT (Treating to New Targets) study investigates the effects of intensive lipid lowering with atorvastatin in patients with coronary heart disease (CHD) with and without pre-existing chronic kidney disease (CKD).

**BACKGROUND:** Cardiovascular disease is a major cause of morbidity and mortality in patients with CKD. **METHODS:** A total of 10,001 patients with CHD were randomized to double-blind therapy with atorvastatin 80 mg/day or 10 mg/day. Patients with CKD were identified at baseline on the basis of an estimated glomerular filtration rate (eGFR)  $< 60$  ml/min/1.73 m<sup>2</sup> using the Modification of Diet in Renal Disease equation. The primary efficacy outcome was time to first major cardiovascular event. **RESULTS:** Of 9,656 patients with complete renal data, 3,107 had CKD at baseline and demonstrated greater cardiovascular comorbidity than those with normal eGFR ( $n = 6,549$ ). After a median follow-up of 5.0 years, 351 patients with CKD (11.3%) experienced a major cardiovascular event, compared with 561 patients with normal eGFR (8.6%) (hazard ratio [HR] = 1.35; 95% confidence interval [CI] 1.18 to 1.54;  $p < 0.0001$ ). Compared with atorvastatin 10 mg, atorvastatin 80 mg reduced the relative risk of major cardiovascular events by 32% in patients with CKD (HR = 0.68; 95% CI 0.55 to 0.84;  $p = 0.0003$ ) and 15% in patients with normal eGFR (HR = 0.85; 95% CI 0.72 to 1.00;  $p = 0.049$ ). Both doses of atorvastatin were well tolerated in patients with CKD. **CONCLUSIONS:** Aggressive lipid lowering with atorvastatin 80 mg was both safe and effective in reducing the excess of cardiovascular events in a high-risk population with CKD and CHD.

Shepherd, J., J. J. Kastelein, et al. (2007). "Effect of intensive lipid lowering with atorvastatin on renal function in patients with coronary heart disease: the Treating to New Targets (TNT) study.[see comment]." *Clinical Journal of The American Society of Nephrology: CJASN* 2(6): 1131-9.

**BACKGROUND AND OBJECTIVES:** Data suggest that atorvastatin may be nephroprotective. This subanalysis of the Treating to New Targets study investigated how intensive lipid lowering with 80 mg of atorvastatin affects renal function when compared with 10 mg in patients with coronary heart disease. **DESIGN, SETTING, PARTICIPANTS, & MEASUREMENTS:** A total of 10,001 patients with coronary heart disease and LDL cholesterol levels of  $< 130$  mg/dl were randomly assigned to double-blind therapy with 10 or 80 mg/d atorvastatin. Estimated GFR using the Modification of Diet in Renal Disease equation was compared at baseline and at the end of follow-up in 9656 participants with complete renal data. **RESULTS:** Mean estimated GFR at baseline was 65.6  $\pm$  11.4 ml/min per 1.73 m<sup>2</sup> in the 10-mg group and 65.0  $\pm$  11.2 ml/min per

1.73 m<sup>2</sup> in the 80-mg group. At the end of follow-up (median time to final creatinine measurement 59.5 months), mean change in estimated GFR showed an increase of 3.5 +/- 0.14 ml/min per 1.73 m<sup>2</sup> with 10 mg and 5.2 +/- 0.14 ml/min per 1.73 m<sup>2</sup> with 80 mg (P < 0.0001 for treatment difference). In the 80-mg arm, estimated GFR improved to > or = 60 ml/min per 1.73 m<sup>2</sup> in significantly more patients and declined to < 60 ml/min per 1.73 m<sup>2</sup> in significantly fewer patients than in the 10-mg arm. CONCLUSIONS: The expected 5-yr decline in renal function was not observed. Estimated GFR improved in both treatment groups but was significantly greater with 80 mg than with 10 mg, suggesting this benefit may be dosage related.

Shepherd, J., J. P. Kastelein, et al. (2008). "Intensive lipid lowering with atorvastatin in patients with coronary artery disease, diabetes, and chronic kidney disease.[see comment]." Mayo Clinic Proceedings 83(8): 870-9.

OBJECTIVE: To investigate the effect of intensive lipid lowering with high-dose atorvastatin on the incidence of major cardiovascular events compared with low-dose atorvastatin in patients with coronary artery disease and type 2 diabetes, with and without chronic kidney disease (CKD). PATIENTS AND METHODS: Following 8 weeks' open-label therapy with atorvastatin (10 mg/d), 10,001 patients with coronary artery disease were randomized to receive double-blind therapy with either 80 mg/d or 10 mg/d of atorvastatin between July 1, 1998, and December 31, 1999. Of 1501 patients with diabetes, renal data were available for 1431. Patients with CKD were defined as having a baseline estimated glomerular filtration rate (eGFR) below 60 mL/min per 1.73 m<sup>2</sup>, using the Modification of Diet in Renal Disease equation. RESULTS: After a median follow-up of 4.8 years, 95 (17.4%) of 546 patients with diabetes and CKD experienced a major cardiovascular event vs 119 (13.4%) of 885 patients with diabetes and normal eGFRs (hazard ratio [HR], 1.32; 95% confidence interval [CI], 1.00-1.72; P<.05). Compared with 10 mg of atorvastatin, 80 mg of atorvastatin reduced the relative risk of major cardiovascular events by 35% in patients with diabetes and CKD (20.9% [57/273] vs 13.9% [38/273]; HR, 0.65; 95% CI, 0.43-0.98; P=.04) and by 10% in patients with diabetes and normal eGFR (14.1% [62/441] vs 12.8% [57/444]; HR, 0.90; 95% CI, 0.63-1.29; P=.56). The absolute risk reduction in patients with diabetes and CKD was substantial, yielding a number needed to treat of 14 to prevent 1 major cardiovascular event over 4.8 years. Both treatments were well tolerated. CONCLUSION: Patients with diabetes, stable coronary artery disease, and mild to moderate CKD experience marked reduction in cardiovascular events with intensive lipid lowering, in contrast to previous observations in patients with diabetes and end-stage renal disease. Trial Registration:clinicaltrials.gov identifier: NCT00327691.

Vrtovec, B., R. Okrajsek, et al. (2008). "Atorvastatin therapy may reduce the incidence of sudden cardiac death in patients with advanced chronic heart failure." Journal of Cardiac Failure 14(2): 140-4.

BACKGROUND: In retrospective studies, statin therapy has been related to decreased incidence of sudden cardiac death (SCD) in heart failure. We sought to prospectively investigate a relation between atorvastatin therapy and SCD in patients with advanced chronic heart failure. METHODS AND RESULTS: We enrolled 110 patients with heart failure with a left ventricular ejection fraction less than 30% and cholesterol level greater than 150 mg/dL. Fifty-five patients were randomized to atorvastatin (10 mg/day) (statin

group); the remaining 55 patients received no statins (controls). Patients were followed for 1 year. At baseline, the two groups did not differ in age, sex, left ventricular ejection fraction, cholesterol, B-type natriuretic peptide, heart rate variability, or QT variability. During follow-up, 29 patients died (26%) and 2 patients (2%) underwent heart transplantation. Of the 29 deaths, 13 were attributed to pump failure, 15 were attributed to SCD, and 1 was attributed to noncardiac causes. All-cause mortality was lower in the statin group (9/55, 16%) than in controls (20/55, 36%) ( $P = .017$ ). The same was true of the SCD rate (3/55 [5%] vs. 12/55 [22%],  $P = .012$ ), but not of the pump failure (5/55 [9%] vs. 8/55 [15%];  $P = .38$ ). SCD-free survival was 2.3-times higher in the statin group than in controls ( $P = .01$ ). CONCLUSIONS: Atorvastatin therapy seems to be associated with decreased incidence of SCD in patients with advanced chronic heart failure. Larger studies are ongoing to confirm this hypothesis.

Wenger, N. K., S. J. Lewis, et al. (2008). "Beneficial effects of aggressive low-density lipoprotein cholesterol lowering in women with stable coronary heart disease in the Treating to New Targets (TNT) study." *Heart* 94(4): 434-9.

OBJECTIVE: To examine by secondary analysis of the Treating to New Targets (TNT) study whether the benefits of intensive versus standard levels of lipid lowering are equally applicable to women. METHODS: A total of 10 001 patients (1902 women) with stable coronary heart disease (CHD) were randomised to double-blind treatment with atorvastatin 10 or 80 mg/day for a median follow-up of 4.9 years. RESULTS: In women and men, intensive treatment with atorvastatin 80 mg significantly reduced the rate of major cardiovascular events compared with atorvastatin 10 mg. Among women, the relative and absolute reductions were 27% and 2.7%, respectively (hazard ratio (HR) = 0.73, 95% confidence interval (CI) 0.54 to 1.00,  $p = 0.049$ ). In men, the corresponding rate reductions were 21% and 2.2% (HR = 0.79, 95% CI 0.69 to 0.91,  $p = 0.001$ ). The number needed to treat value (to prevent one cardiovascular event over 4.9 years compared with patients treated with atorvastatin 10 mg) for atorvastatin 80 mg was 29 for women and 30 for men. Rates of death of non-cardiovascular origin in the atorvastatin 80 mg and atorvastatin 10 mg were 3.6% and 1.6%, respectively ( $p = 0.004$ ) among women, and 2.8% and 3.1% ( $p = 0.47$ ) among men. CONCLUSION: Intensive lipid-lowering treatment with atorvastatin 80 mg produced significant reductions in relative risk for major cardiovascular events compared with atorvastatin 10 mg in both women and men with stable CHD.

Zhu, J. R., B. Tomlinson, et al. (2007). "A randomised study comparing the efficacy and safety of rosuvastatin with atorvastatin for achieving lipid goals in clinical practice in Asian patients at high risk of cardiovascular disease (DISCOVERY-Asia study)." *Current Medical Research & Opinion* 23(12): 3055-68.

BACKGROUND: Most studies investigating the benefits of statins have focused on North American and European populations. This study focuses on evaluating the lipid-lowering effects of rosuvastatin and atorvastatin in Asian patients. OBJECTIVES: The Direct Statin Comparison of LDL-C Values: an Evaluation of Rosuvastatin therapy (DISCOVERY)-Asia study is one of nine independently powered studies assessing the efficacy of starting doses of statins in achieving target lipid levels in different countries worldwide. DISCOVERY-Asia was a 12-week, randomised, open-label, parallel-group study conducted in China, Hong Kong, Korea, Malaysia, Taiwan, and Thailand.