

A summary of

The Report of the National Lipid Association Statin Safety Task Force

James McKenney, PharmD, Ed.

— Am J Cardiol. 2006;97:Supplement

and

International Studies on the Comparative Safety of Rosuvastatin

Johansson S, Ming EE, Wallander M, et al.

— Pharmacoepidemiol Drug Saf. 2006 May 30 [Epub ahead of print]

McAfee AT, Ming EE, Seeger JD, et al.

— Pharmacoepidemiol Drug Saf. 2006 June 8 [Epub ahead of print]

Goettsch WG, Heintjes EM, Kastelein JJP, et al.

— Pharmacoepidemiol Drug Saf. 2006 June 8 [Epub ahead of print]

*With a managed care analysis by Steven R. Peskin, MD, MBA,
former medical director for Cigna and PacifiCare*

ABSTRACT

The National Lipid Association (NLA) Statin Safety Task Force Report provides a comprehensive evaluation of adverse events (AEs) associated with the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins). Experts in liver, muscle, and kidney, address the safety of statins and make NLA recommendations on their use. The Task Force concludes that statins have been proven safe and that all currently marketed statins have a similar low risk of serious AEs. Separately, investigators leading a series of comprehensive pharmacoepidemiology programs to evaluate the safety of rosuvastatin conclude that this agent has a safety profile comparable to other currently marketed statins. For managed care decision makers, the two reports provide important considerations for building a formulary that includes safe and effective brand-name statins.



Report of the NLA Statin Safety Task Force

The National Lipid Association Statin Safety Task Force report provides a comprehensive evaluation of statin safety. The Task Force, commissioned by a multidisciplinary, not-for-profit association of health care professionals who manage patients with lipid disorders and increased cardiovascular risk, concluded that all currently marketed statins are safe and share a similar low risk of serious adverse events.

Available for nearly two decades, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) have become an essential part of risk-reduction therapy for coronary artery disease (CAD). Although their efficacy is well established, concerns about the side effects and risks of statin therapy have arisen, largely as a result of publicity surrounding the market withdrawal of cerivastatin because of serious adverse events (AEs).

To address these concerns, the National Lipid Association (NLA) recently convened a Safety Task Force to undertake an intensive unbiased evaluation of statin safety, with a specific focus on the effects of statins on muscle, liver, and kidneys. The Task Force report — published as a supplement to the *American Journal of Cardiology* — reflects a rigorous review of the literature on adverse reactions and drug interactions, a meta-analysis of randomized clinical trials, an analysis of managed care databases, an analysis of the U.S. Food and Drug Administration's Adverse Events Reporting System (AERS) database, and a review of data from new drug application (NDA) submissions. The Task Force also appointed experts in liver, muscle, and kidney function to evaluate the safety of statins and provide recommendations for their use.

Drug interactions

The Task Force found there is a significant increase in the risk of muscle AEs when interacting drugs are added to a patient's statin regimen.¹ The mechanism for most statin-drug interactions involves the cytochrome P450 3A4 (CYP3A4) isoenzyme. Studies of drug metabolism show that simvastatin and lovastatin are particularly sensitive to CYP 3A4 inhibitors, whereas atorvastatin metabolism is less affected.¹ In addition, possibly by inhibiting statin biliary excretion and glucuronidation, gemfibrozil administered along with rosuvastatin, lovastatin, and simvastatin significantly increases myopathy and rhabdomyolysis risk.¹

Safety assessment using an administrative claims database

The Task Force conducted a retrospective observational study, culling information from a database of 9 million commercial managed care members.² Results of this study support earlier research findings that statin monotherapy is safe and well tolerated. Increased risk of AEs were associated with certain comorbid conditions, including diabetes and hypertension; specific combination therapies (e.g., gemfibrozil); and giving CYP3A4 inhibitors concomitantly with statins.²

An appraisal from the Adverse Event Reporting System

With respect to statins, the Task Force found that the reporting of AEs has been influenced by several biases, including product withdrawals and adverse publicity in the lay and medical press.³ Reporting patterns for rosuvastatin are similar to those of other well-established statins. The Task Force found this report-proportion metric particularly reassuring with respect to rosuvastatin, because in the case of cerivastatin, reporting of key AEs did not follow patterns similar to those for other statins available at the time.³ In the United States, rhabdomyolysis reports for rosuvastatin are at rates that are consistent with its preapproval safety database and with other statins currently on the market (Table 1).⁴

TABLE 1 Muscle toxicity in rosuvastatin NDA
5–40 mg dose clinical trials

Dose (mg)	Patients	CK >10 ULN and muscle side effects		Rhabdomyolysis CK >10 ULN and renal changes	
		(n)	%	(n)	%
5	1,324	3	0.2	0	0
10	8,325	10	0.1	0	0
20	4,651	8	0.2	1	0.2
40	4,450	8	0.2	0	0
All doses	13,395	29	0.2	1	0.007

CK=creatinine kinase; ULN=upper limits of normal.
SOURCE: FDA 2005¹²

Liver safety: key messages and recommendations

Key messages from the Liver Expert Panel are summarized in Table 2.

Recommendations

Although routine monitoring of patients taking statin therapy is unnecessary, the Liver Expert Panel recommends that clinicians be alert to patient reports of jaundice, malaise, fatigue, lethargy, and related symptoms as a signal of potential hepatotoxicity. Fractionated bilirubin, rather than isolated aminotransferase levels, should be used to determine significant liver injury. If the clinician identifies objective evidence of significant liver injury, the statin should be discontinued.⁵ If an isolated asymptomatic transaminase level is 1–3 times the upper limits of normal (ULN), statin therapy does not need to be discontinued. If this level is >3 times ULN during routine evaluation, the test should be repeated; if still elevated, other causes should be ruled out first.⁶ It is safe to administer statin therapy to patients with chronic liver disease, compensated cirrhosis, nonalcoholic fatty liver disease, or nonalcoholic steatohepatitis.⁵

Muscle safety

Key messages from the Muscle Expert Panel are summarized in Table 3. The risk of drug-related muscle injury is approximately the same for all currently marketed statins. The spectrum of reported muscle AEs appears to be a class effect, but the AEs are rarely severe, and it is also rare that these events would progress to a life-threatening situation.⁶ Among statins, cerivastatin represented a unique set of circumstances; it had an unfavorable pharmacokinetic profile and the potential for multiple drug interactions. In addition, it was made available at a dose higher than was deemed safe.⁶

The Muscle Expert Panel backed the generally accepted and widely used definition of *myopathy* (muscle pain, soreness, weakness, and/or cramps plus a creatinine kinase (CK) level >10 times the ULN).⁶ It suggested a new definition for *rhabdomyolysis*, however, in an attempt to integrate existing definitions and identify the clinical situation where the risk of acute renal failure is high. To be consistent with the FDA's definition, the expert panel chose a CK level of >10,000 U/L regardless of a change in renal function.⁶

Recommendations

When patients taking statins present with muscle symptoms or an increased CK level, an attempt should be made to rule out other causes. A pretreatment baseline CK level may be obtained in patients at high risk for muscle toxicity; e.g., older individuals, or when combining a statin with an agent known to increase myotoxicity. CK measurement in asymptomatic patients during statin therapy is not required, but measurement should

TABLE 2 Liver Expert Panel: key messages

- There is no proof that statins cause life-threatening liver damage.¹⁰
- Mild asymptomatic elevations in liver enzymes are found in about 3 patients per 1,000 person-years who participate in clinical trials. Elevations are reversible on stopping the statin and do not cause lasting harm.⁶
- Liver failure has been reported in 1 person out of 1 million person-years of statin use, as well as in 1 person in 1 million people not taking a statin.¹¹
- Routine liver function monitoring during statin therapy is not needed. The Task Force recommends that statin manufacturers work with the FDA to remove the requirement for liver function monitoring from prescribing information.⁶

TABLE 3 Muscle Expert Panel: key messages

- Though all marketed statins have a small potential for inducing muscle side effects, 5 in 100,000 patients taking a statin have muscle complaints and are found to have an increase in muscle enzymes, suggesting muscle injury. This finding is not statistically significant.¹¹
- 1.5–3.0 percent of patients taking a statin complain of muscle pain, weakness, or cramps. The numbers are similar for patients receiving placebo.⁶
- Exercise, trauma, falls, accidents, seizures, infections, chills, and alcohol and drug abuse can cause muscle injury. Physicians should carefully identify and address the risk factors for muscle problems before prescribing a statin.⁶
- Rhabdomyolysis, the most serious potential problem associated with statin therapy, occurs in about 2 of 100,000 patients taking a statin. This is rarely life threatening and is reversible when the statin is stopped.¹¹

be obtained in symptomatic patients to gauge the severity of muscle damage and to facilitate treatment decisions.⁶

When other causes have been ruled out, patients with intolerable muscle symptoms should discontinue statin therapy. When symptoms are no longer present, the patient can be started on the same statin or a different one at an equivalent or lower dose, and the clinician should watch for a repeat of symptoms. If a patient experiences

**TABLE 4 Kidney Expert Panel:
key messages**

- The panel found no evidence that statins, when taken in approved doses, cause kidney injury.⁷
- Protein may be found in the urine of patients receiving a statin as frequently as it is found in the urine of patients who do not receive a statin.⁶
- If protein is found in the urine of patients who are taking a statin, it is not necessary to discontinue the statin.⁶
- If kidney function worsens in patients taking a statin, discontinuation is not necessary, although a dose adjustment may be indicated.⁶

symptoms with several different statins and doses, an alternative lipid-lowering therapy is recommended. Patients with tolerable muscle complaints, or who are asymptomatic with a CK <10 times ULN, may continue statin therapy at the same or reduced doses. Statin therapy should be discontinued in patients who develop rhabdomyolysis. Once the patient has recovered, the therapeutic risk-to-benefit ratio should be carefully considered.⁶

Kidney safety

Key messages from the Kidney Expert Panel are summarized in Table 4. The panel concluded that in the absence of rhabdomyolysis, statin use does not lead to acute renal failure or insufficiency.⁷ In addition, in more than 10,000 patients with and without diabetes who received open-label rosuvastatin for up to 3.8 years, no progressive decline in renal function was found; rather, serum creatinine and GFR values improved, thus suggesting a potential renal-protective effect with statins. More research is needed to confirm this finding, however.^{6,8} The panel also noted that in the most comprehensive analysis to date, involving 38 reports of renal failure or insufficiency in patients receiving rosuvastatin, an FDA review found no evidence to link statin therapy with serious renal injury.⁶

In the opinion of the Renal Expert Panel, statins do not cause proteinuria in humans.⁷ The frequency of proteinuria found with rosuvastatin (5–40 mg) was no different than that found with placebo. The same was found in patients taking marketed doses of atorvastatin, pravastatin, and simvastatin.⁹ Other evaluations support the suggestion that the proteinuria observed with statin therapy results from physiologic interference with protein

uptake in renal tubules.⁹ These studies also illustrate that proteinuria is possible with all statins, but is more likely to be seen with potent inhibitors of HMG-CoA reductase.⁹

Recommendations

Routine serum CK and proteinuria monitoring is not required during statin therapy, although an assessment of renal function is advisable prior to starting therapy. If serum CK becomes elevated in a patient without rhabdomyolysis, the statin generally does not need to be withdrawn, but a dose adjustment may be necessary. If proteinuria develops, an investigation into the cause of proteinuria is warranted. Although chronic kidney disease does not preclude statin use, in cases of moderate or severe renal insufficiency, dosage adjustment may be necessary.⁶

Conclusion

Based on the available data, the NLA Statin Safety Task Force has concluded that all currently marketed statins are safe and share a low risk of serious AEs. Any possible risks are greatly outweighed by their protective effects against thromboembolic stroke and CAD.

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International Studies Affirm Rosuvastatin Safety Relative to Other Currently Marketed Statins

In a series of reports in *Pharmacoepidemiology and Drug Safety*, Johansson describes the rationale and methodology of a rosuvastatin pharmacoepidemiology program as part of the manufacturer's assessment of its benefit-risk profile; McAfee finds that rosuvastatin safety is comparable to others now on the U.S. market; and Goettsch reports on adverse events outcomes in a Dutch study of patients taking rosuvastatin.

Pharmacoepidemiology studies complement randomized clinical trials and spontaneous reporting systems through their ability to study large heterogeneous groups of people for an extended period of time. This approach allows investigators to estimate drug effectiveness and incidence of adverse events (AEs) in the general population, study delayed drug effects or events too common to be detected adequately by spontaneous reporting systems (SRS), and observe uncommon drug effects and interactions with other drugs. These data, which are collected in clinical practice settings, allow pharmaceutical products to be evaluated in real-life situations — such as in patients who are being treated for concomitant conditions and who take multiple prescription and nonprescription products — and also provide important safety signals.¹

The goal of the rosuvastatin pharmacoepidemiology program was to augment data obtained from clinical trials and SRS. It sought to provide real-life data on patient characteristics and AEs in patients taking rosuvastatin compared with those taking other statins, based on reviews of existing databases and medical records. This article provides an overview of the program rationale, study methodology, and reports of results from the United States and other sites.

Investigators from the U.S. arm of the program found no difference between rosuvastatin and other statins in terms of liver- and kidney-related hospitalizations or death.² Similarly, European investigators found the muscle, kidney, and liver safety profiles of rosuvastatin to be similar to other statins.³

Program design

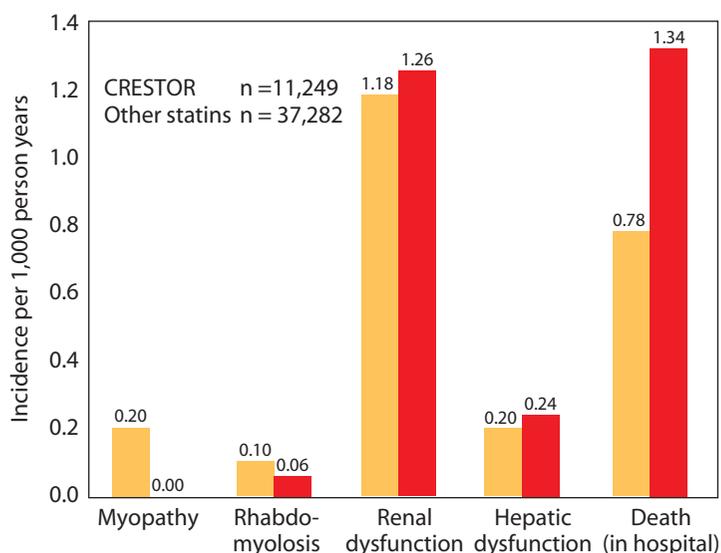
The rosuvastatin pharmacoepidemiology program consisted of prospective cohort studies that followed statin users over time to approximate incidence rates, attributable risks, and relative risks for AEs. Prescribing physicians were unaware of the study at the time of treatment so that the study investigator had no influence on treatment selection.¹ Studies were conducted in recognized centers of excellence.¹

The program consisted of nine studies — four patient-characteristics studies, four safety-evaluation studies, and a prescription-event monitoring [PEM] study — conducted in four countries: United States (US), the Netherlands, United Kingdom (UK), and Canada.

The four patient-characteristic studies included descriptions of drug-utilization patterns of new rosuvastatin users compared with new users of other statins in the four countries. These studies recorded demographics, diagnoses, comorbidities, healthcare use, concomitant medication, statin dose, prior statin use, and lipid levels. Each of the four studies conducted between 2003 and 2005 followed new users in the first 1 to 2 years of rosuvastatin availability in each country. The studies collected data from more than 325,000 statin-treated patients, with most (approximately 220,000) from the United States.¹

The four safety-evaluation studies examined rates of specific events among all statin users and determined risk factors for these events. In each of the studies, patients were monitored for death or hospitalization for specified mus-

Results from U.S. pharmacoepidemiological study



SOURCE: MCAFEE 2006²

cle, renal, or hepatic events, and AE incidence rates were compared for each statin. To ensure comparability of results, the four safety studies were conducted in similar fashion. Patients were taken from the same databases used for the characteristics studies. The numbers of patients followed in each study varied; about 50,000 each were included in the both the U.S. and Netherlands studies.¹

The PEM study was a noninterventional, observational study intended to examine the safety of rosuvastatin in general medical practice in England.¹ Through a survey of general practitioners, the PEM also attempted to quantify the incidence of both frequently and rarely reported events, as well as previously unrecognized adverse drug reactions. This study was designed and conducted independently by the Drug Safety Research Unit, a research charity affiliated with the University of Portsmouth in the United Kingdom.¹

Databases

The well-established databases used in the pharmacoepidemiology program offer information on comorbidities, concomitant prescriptions, and hospitalizations. They encompass large populations and thus can provide the “critical mass” needed to generate meaningful results, even with respect to rare events.¹

The US study was based on the comprehensive administrative databases of one of the largest commercial health insurers in the country, and included medical and pharmacy claims data on 10 million people per year. Patients were followed for as long as they are continuously enrolled. In the Dutch, Canadian, and British studies, government databases containing patient records provided a rigorous and robust basis for analysis.¹

Results

To date, results are available from the US and the Netherlands safety-evaluation studies, and the UK PEM.

United States: matched cohort study

The U.S. pharmacoepidemiology study followed more than 48,000 statin-treated patients (rosuvastatin initiators, $n=11,249$; other statin initiators, $n=37,282$) for up to 18 months. The incidence rate (IR) per 1,000 person-years for myopathy, rhabdomyolysis, renal dysfunction, and hepatic dysfunction are depicted in the Figure on page 5. Statistically, no differences were observed between rosuvastatin and other statins in terms of hospitalizations associated with renal or hepatic events, even after controlling for baseline statin use, age, and gender.² The IR for renal dysfunction was 1.18 for rosuvastatin initiators ($n=12$) and 1.26 for other statin initiators ($n=42$). For hepatic dysfunction, the IR was 0.20 for rosuvastatin initiators ($n=2$) and 0.24 for other statin initiators ($n=8$).²

McAfee et al. characterize the absolute IRs for rhabdomyolysis and myopathy as “reassuringly low” among all

statin initiators, but too small for conclusive comparisons to be drawn.²

It was noted that in-hospital mortality for patients taking rosuvastatin was half that among patients taking other statins, though these findings are not statistically significant. The authors theorize that this outcome could have resulted from “subtle but important” changes in patients’ characteristics that influenced their risk of dying.²

The Netherlands: PHARMO

The Netherlands pharmacoepidemiology study results provided similar reassurance on rosuvastatin safety. This study followed 10,147 patients treated with rosuvastatin and 37,396 patients treated with other statins for up to 24 months. The incidence of rhabdomyolysis, myopathy, acute renal failure, and hepatic impairment in statin users was <1 in 3,000 person-years exposure to statins. The results did not show a significant increase in incidence of rhabdomyolysis, myopathy, acute renal failure, and hepatic impairment in rosuvastatin relative to other statins.³

Both the US and Netherlands studies found overall low incidence of rhabdomyolysis and myopathy, acute renal failure, and hepatic impairment, and no differences between the individual statins. These results corroborate findings of clinical trials indicating that serious AEs are uncommon in statin users and do not significantly differ among the currently available statins.³

United Kingdom: PEM

The PEM study observed 11,680 patients (median age 64 years; 50.3 percent male) for a median duration of 10 months identified by the English Prescription Pricing Authority as having had a prescription for rosuvastatin dispensed. The most common rosuvastatin dose prescribed was 10 mg (84 percent).⁴ Rosuvastatin was generally well tolerated and there were no cases of rhabdomyolysis. No new signals for AEs were observed. Of patients who stopped rosuvastatin treatment, the most common reasons for discontinuation were myalgia (13.5 percent), patient request (7.0 percent), and adverse publicity regarding the drug (6.0 percent).

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Conclusions: NLA Statin Safety Task Force and pharmacoepidemiology studies

- NLA panel determines that currently marketed statins are safe and have a similar, low risk of adverse events
- Investigation by NLA Task Force confirms safety profile of rosuvastatin is comparable to other statins
- US and Dutch pharmacoepidemiology studies of 100,000 patients taking a statin — including more than 20,000 taking rosuvastatin — found safety profile of rosuvastatin similar to that of other marketed statins
- Consistency of findings among these studies — together with results of PEM study, rosuvastatin clinical trial program, and spontaneous reporting data — reinforce the strong safety profile of rosuvastatin

Managed Care Considerations: Safe and Effective Means for Addressing A Major Public Health Threat

By Steven R. Peskin, MD, MBA

For clinical executives, statin safety is an important consideration for the relatively large subpopulation of health plan members that should be on lipid-lowering therapy.

To address this concern, the National Lipid Association, a multidisciplinary, not-for-profit membership association of healthcare professionals who manage patients with lipid disorders, created a Statin Safety Task Force. The committee's findings, published in a supplement to the *American Journal of Cardiology*, are reassuring.

The most widely publicized adverse events, myopathy and rhabdomyolysis, occur rarely. For myopathy, the outcome is 5 patients per 100,000 person years; for rhabdomyolysis, the occurrence is 1.6 patients per 100,000 person years. Of note, the risk of drug-related muscle injury is approximately the same for all currently marketed statins.

Regarding hepatic-related side effects, the NLA's Liver Expert

Panel concluded that statins pose extremely low risk and that routine liver enzyme monitoring is not necessary. In the absence of rhabdomyolysis, renal failure or insufficiency does not appear to be caused by statins.

These findings hold equally for the newest statin, rosuvastatin. In addition to the comparator information for rosuvastatin in the NLA report, a recent series of studies published in *Pharmacoepidemiology and Drug Safety* analyze data from nine studies conducted in four countries. These pharmacoepidemiologic studies of rosuvastatin safety — using multiple methods of rigorous retrospective analysis from diverse populations — longitudinally demonstrate that the rosuvastatin safety profile is similar to that of other statins.

For health plan executives, safety is a primary concern when considering formulary acceptance. The research described herein provides valuable evidence of the

safety of effective branded statins. With the introduction of generic, low-strength statins, these findings are all the more important. Given the relative strength of rosuvastatin and the revised ATP-3 recommendations encouraging clinicians to help their patients achieve lower levels of LDL cholesterol in populations with prior cardiovascular events or certain risk profiles, health plan clinical executives should weigh the relative benefits against the relative risks to optimize outcomes for populations that are at risk for CV events.

A former medical director for Cigna and PacifiCare, Steven R. Peskin, MD, MBA, has more than 10 years' commercial health plan/payer and Medicare managed care experience. Peskin is currently chief medical officer for MediMedia USA. He is an assistant clinical professor of medicine at the University of Medicine and Dentistry of New Jersey and is clinical scholar in the Department of Health Policy at Thomas Jefferson University School of Medicine in Philadelphia.



Steven R. Peskin,
MD, MBA