

The Safety of Rosuvastatin as Used in Common Clinical Practice A Postmarketing Analysis

Alawi A. Alsheikh-Ali, MD; Marietta S. Ambrose, MD; Jeffrey T. Kuvin, MD; Richard H. Karas, MD, PhD

Background—Statins are currently the mainstay of dyslipidemia management for the primary and secondary prevention of cardiovascular disease. Controversial concerns about the safety of the newly marketed statin rosuvastatin have been raised on the basis of premarketing studies and a few postmarketing reports.

Methods and Results—We reviewed rosuvastatin-associated adverse events reported to the US Food and Drug Administration over its first year of marketing. On the basis of prescription data obtained from IMS Health, rates of adverse event reports (AERs) per million prescriptions were calculated. Rates of rosuvastatin-associated AERs over its first year of marketing were compared with those seen with atorvastatin, simvastatin, and pravastatin over the concurrent timeframe and during their respective first years of marketing. Comparison was also made to the first year of marketing of cerivastatin. The primary analysis examined the composite end point of AERs of rhabdomyolysis, proteinuria, nephropathy, or renal failure. With either timeframe comparison, rosuvastatin was significantly more likely to be associated with the composite end point of rhabdomyolysis, proteinuria, nephropathy, or renal failure AERs. Reported cases of rhabdomyolysis, proteinuria, or renal failure tended to occur early after the initiation of therapy and at relatively modest doses of rosuvastatin. The increased rate of rosuvastatin-associated AERs relative to other widely used statins was also observed in secondary analyses when other categories of AERs were examined, including adverse events with serious outcomes, liver toxicity, and muscle toxicity without rhabdomyolysis.

Conclusions—The present analysis supports concerns about the relative safety of rosuvastatin at the range of doses used in common clinical practice in the general population. (*Circulation*. 2005;111:0000-0000.)

Key Words: cholesterol ■ complications ■ drugs ■ lipids ■ population

Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (statins) are currently the mainstay of dyslipidemia management for the primary and secondary prevention of cardiovascular disease.¹ Their widespread use is driven by a robust body of evidence supporting their efficacy in preventing cardiovascular events.¹ Recent data have shown that more intensive lipid lowering with high-dose statins offers additional benefit.²⁻⁶ This finding has intensified interest in more potent statins that could better achieve the more aggressive LDL cholesterol (LDL-C) targets.

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Of the currently available statins, rosuvastatin has the greatest effect on LDL-C.⁷ Although its potency can be an advantage, controversial concerns have been raised about its safety, particularly in terms of rhabdomyolysis and renal failure, on the basis of premarketing studies and a few postmarketing reports.⁸⁻¹³ Given previous concerns about the safety of the potent statin cerivastatin that eventually led to its

withdrawal from the global market, it is essential to assess the postmarketing safety of rosuvastatin relative to other widely used drugs in this class. Such assessment either can serve to alleviate concerns about the safety of rosuvastatin and hence encourage its appropriate use in patients who need it or can detect an adverse safety profile that was not fully appreciated in premarketing trials.¹⁴

In the present analysis, using a methodology we have previously used to assess postmarketing safety of lipid-altering drugs,¹⁵⁻¹⁸ we reviewed adverse event reports (AERs) to the US Food and Drug Administration (FDA) to determine the frequency of rosuvastatin-associated events relative to other commonly used statins.

Methods

Using a computer-based search engine (DrugLogic, QED Solutions), we reviewed AERs to the FDA in which rosuvastatin was listed as a suspect in causing the adverse event. The search engine includes 2 FDA databases, the Spontaneous Reporting System (1969-1997) and the Adverse Events Reporting System (1997 on), both of which

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TABLE 1. Demographic Characteristics of Individuals With AERS of Rhabdomyolysis, Proteinuria/Nephropathy, or Renal Failure (COMPOSITE AERS) Associated With Rosuvastatin, Simvastatin, Pravastatin, or Atorvastatin and Received by the US FDA Between October 1, 2003, and September 30, 2004

	Rosuvastatin (n=145)	Simvastatin (n=381)	Pravastatin (n=52)	Atorvastatin (n=315)
Prescriptions, in millions	5.2	29.8	15.0	72.9
Age, y	59.6±1.3	65.3±0.8†	66.3±1.5‡	62.1±0.9
Male, %	55	63	69	46
Statin dose, mg	16.7±1.2	53.1±2.8†	18.8±2.0	21.8±1.4*
Duration of therapy, d	69.8±7.8	731.3±68.4†	744.7±228.7†	368.8±46.0†
Other concomitant medications, n	4.2±0.3	5.0±0.4	6.2±0.8*	5.7±0.4
Outcome, %				
Death	2	6	15‡	10‡
Hospitalization	72	76	83	66
No hospitalization	26	18	2†	24

Continuous variables are presented as mean±SE. Some reports listed both hospitalization and death as an outcome.

* $P<0.05$, † $P<0.001$, ‡ $P<0.01$ for pairwise comparison versus rosuvastatin.

rely on reports generated by health professionals, consumers, and manufacturers.

For comparative purposes, we evaluated 4 other statins: atorvastatin, simvastatin, pravastatin, and cerivastatin (during the time period when it was available). In doing so, we compared the postmarketing safety profile of rosuvastatin with other statins, the 3 most widely used with broadly acceptable safety profiles (atorvastatin, simvastatin, and pravastatin) and 1 with an unfavorable safety profile that eventually led to its withdrawal from the global market (cerivastatin).

Two comparative analyses were performed. For the first analysis, AERs were tabulated for the first year during which rosuvastatin was available in the United States (October 1, 2003, the first quarter after launch of rosuvastatin in the United States, to September 30, 2004, the last quarter for which data were available through the search engine) and over this concurrent time period for the other statins. This is referred to as "concurrent time period analysis." The second approach was undertaken to control for the potential of preferential reporting of adverse events with newly marketed drugs.¹⁹ For the second analysis, referred to as "first year of marketing analysis," rates of rosuvastatin-associated AERs were compared with those observed during the first year of marketing for atorvastatin (1997), simvastatin (1992), pravastatin (1992), and cerivastatin (1998).

The number of AERs to the FDA was tabulated for each of the statins. Corresponding prescription data over the time periods of interest were obtained from IMS Health for each of the statins evaluated. Using the tabulated number of AERs and the prescription data, we calculated rates of AERs per 1 million prescriptions for various categories of AERs associated with each of the statins.

Primary Analysis

AERs were categorized according to the specific reaction reported to the FDA. The primary analysis focused on the prespecified, composite end point of AERs of rhabdomyolysis, proteinuria, nephropathy, or renal failure (COMPOSITE AERs). The rate of rosuvastatin-associated COMPOSITE AERs was compared with the rates of such events with the other statins. These specific adverse events were chosen for the primary analysis because they were identified as the primary areas of concern in previous safety analyses of rosuvastatin.

For the concurrent time period analysis, the following characteristics of COMPOSITE AERs were noted: subject age and gender, statin dose and duration of therapy, and outcome of the adverse event classified as death, hospitalization, or no hospitalization. In addition, we noted the number of other concomitant medications and the

concomitant use of a fibric acid derivative or other drugs that can potentially interact with statins.

Secondary Analyses

Comparisons pertaining to the following categories of AERs were performed as secondary analyses: (1) reports of any adverse event (ALL AERs); (2) reports of serious adverse events, defined as fatal, considered life-threatening by the reporter, or resulting in hospitalization (SERIOUS AERs); (3) reports of adverse events affecting the liver (LIVER AERs); (4) reports of adverse events affecting muscle (myalgia, myopathy, elevated creatine-phosphokinase) without frank rhabdomyolysis (MUSCLE-NO-RHABDO AERs); (5) reports of rhabdomyolysis (RHABDO AERs); (6) reports of proteinuria or nephropathy (PROTEINURIA AERs); and (7) reports of renal failure (RENAL FAILURE AERs).

Statistical Analysis

We used χ^2 tests (with appropriate degrees of freedom) to compare rates of AERs among the various statins. For each specific adverse event category, within-group differences (ie, among all the statins examined) were first sought. If within-group differences were not statistically significant, no further analysis was undertaken for that adverse event category. If within-group differences were statistically significant, subsequent pairwise analyses were performed with χ^2 tests. For all analyses, a value of $P<0.01$ was considered statistically significant to account for the multiple comparisons made. For the data in Table 1, continuous variables were compared by use of ANOVA on ranks test for within-group comparisons and the Mann-Whitney rank-sum test for pairwise comparisons to allow for unequal variance among the groups. Categorical variables were compared by use of the χ^2 test. All statistical analyses were performed with SigmaStat 3.10 (Systat Software Inc).

Results

Primary Analysis

In the concurrent time period analysis, the rate of rosuvastatin-associated COMPOSITE AERs (rhabdomyolysis, proteinuria/nephropathy, or renal failure) was higher than simvastatin ($P<0.001$), pravastatin ($P<0.001$), and atorvastatin ($P<0.001$; Figure 1A). A similar pattern was observed with the first year of marketing analysis (Figure 1B). The rate of rosuvastatin-associated COMPOSITE AERs was not sig-

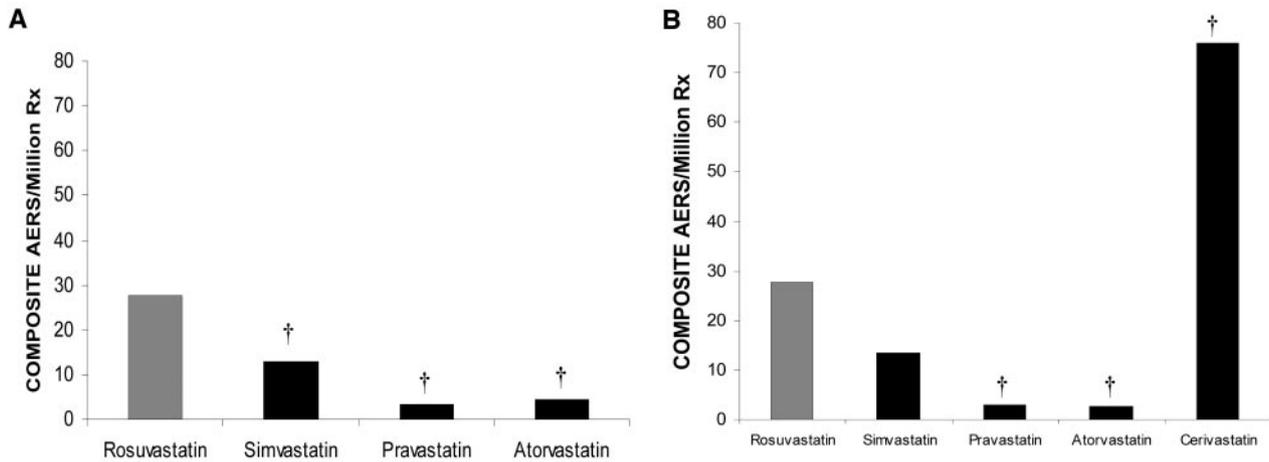


Figure 1. Rates of composite end point of AERs of rhabdomyolysis, proteinuria/nephropathy, or renal failure (COMPOSITE AERs) associated with various statins. A, Rates over concurrent use period from October 1, 2003, to September 30, 2004; B, rates over respective first postmarketing year for each statin. Rates are per 1 million prescriptions (Rx). †*P*<0.001 for pairwise comparison vs rosuvastatin.

nificantly different than simvastatin (*P*=0.02; not considered statistically significant after Bonferroni’s correction) but was significantly higher than pravastatin (*P*<0.001) and atorvastatin (*P*<0.001). Compared with what was observed with cerivastatin during its first postmarketing year, rosuvastatin-associated COMPOSITE AERs were less frequent (*P*<0.001; Figure 1B).

Demographic characteristics of individuals with COMPOSITE AERs are shown in Table 1. The reported adverse events tended to occur in relatively young individuals with no specific gender predominance and at relatively modest doses of statin. Indeed, 62% of the rosuvastatin-associated COMPOSITE AERs occurred at doses of ≤10 mg/d rosuvastatin. Interestingly, the rosuvastatin-associated COMPOSITE AERs occurred early after the initiation of therapy (within the first 12 weeks) compared with the other statins. Although fatal in only a minority of cases, most COMPOSITE AERs listed hospitalization as an outcome. Table 2 lists the mean number of other concomitant medications and the percentage of COMPOSITE AERs in the concurrent time period analysis reporting concomitant use of fibrates or other drugs that can potentially interact with statins. In general, the use of such drugs was relatively rare with rosuvastatin-associated AERs

and tended to be comparable to or less than what was observed with the other statins (Table 2).

Secondary Analyses: Concurrent Time Period

Figure 2 depicts the concurrent time period secondary analyses of rates of AERs from October 1, 2003, to September 30, 2004, for rosuvastatin, simvastatin, pravastatin, and atorvastatin (cerivastatin was no longer available during this time period). The rate of rosuvastatin-associated ALL AERs was higher than simvastatin, pravastatin, and atorvastatin (*P*<0.001 for each statin versus rosuvastatin; Figure 2A). Rosuvastatin-associated SERIOUS AERs, LIVER AERs, and MUSCLE–NO–RHABDO AERs were also more common than each of these AERs associated with simvastatin, pravastatin, or atorvastatin (Figure 2B, 2C, and 2D, respectively; *P*<0.001 for each statin versus rosuvastatin). Moreover, the rate of rosuvastatin-associated RHABDO AERs was higher than RHABDO AERs associated with simvastatin (*P*<0.01; Figure 2E), pravastatin, and atorvastatin (*P*<0.001 for both versus rosuvastatin; Figure 2E). Although reports of proteinuria or nephropathy associated with rosuvastatin were relatively rare (2.7 AERs per 1 million prescriptions), they were significantly more frequent than what was observed with the other statins over the concurrent time period (Figure 2F). A

TABLE 2. Percent of Statin-Associated COMPOSITE AERs (of Rhabdomyolysis, Proteinuria/Nephropathy, or Renal Failure) Listing Concomitant Use of Other Drugs That Can Potentially Interact With Statins in the Concurrent Time Period Analysis From October 1, 2003, to September 30, 2004

	Rosuvastatin (n=145)	Simvastatin (n=381)	Pravastatin (n=52)	Atorvastatin (n=315)
No. of other concomitant medications, mean±SE	4.2±0.3	5.0±0.4	6.2±0.8*	5.7±0.4
Fibric acid derivative (gemfibrozil, fenofibrate, bezafibrate), %	7.6	18.4†	5.8	5.7
Macrolide antibiotic (erythromycin, azithromycin, clarithromycin), %	1.4	5.5	0	4.1
Azole antifungal (fluconazole, itraconazole, ketoconazole), %	0.7	0.8	0	0.6
Cyclosporin, %	1.4	7.9*	1.9	3.8
Calcium channel blocker (amlodipine, diltiazem, verapamil, nifedipine), %	17.2	25.7	30.8	30.2†
Amiodarone, %	2.8	7.3	3.8	2.9

**P*<0.05, †*P*<0.01 for pairwise comparison versus rosuvastatin.

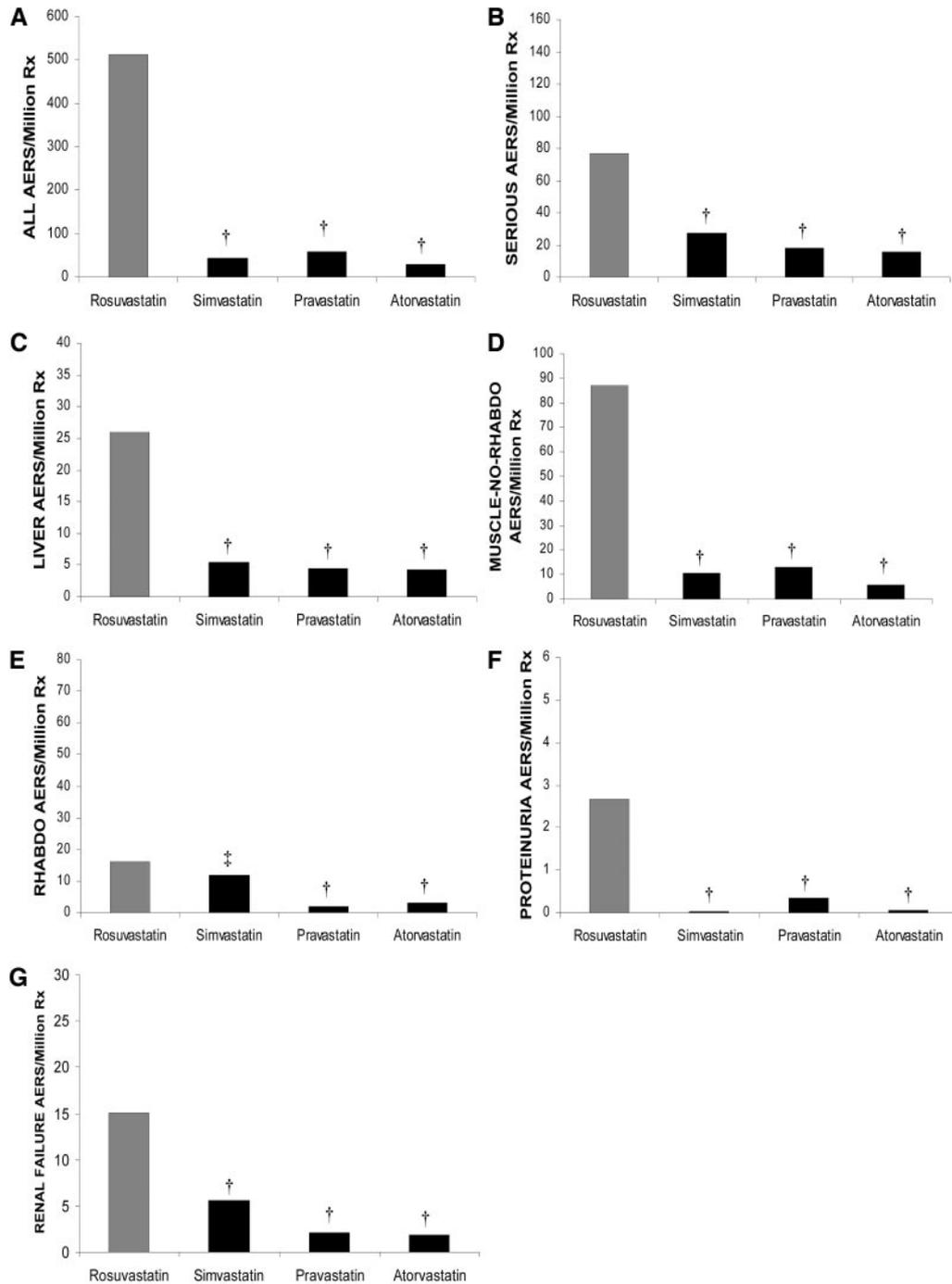


Figure 2. Rates of each category of AERs associated with various statins during concurrent use period from October 1, 2003, to September 30, 2004. A, ALL AERs; B, SERIOUS AERs; C, LIVER AERs; D, MUSCLE-NO-RHABDO AERs; E, RHABDO AERs; F, PROTEINURIA AERs; G, RENAL FAILURE AERs. All rates are per 1 million prescriptions (Rx). Note specific scale on vertical axis for each category of AERs. † $P < 0.001$, ‡ $P < 0.01$ for pairwise comparison vs rosuvastatin.

similar trend was observed with renal failure reports, in which the rate of rosuvastatin-associated RENAL FAILURE AERs was higher than simvastatin-associated RENAL FAILURE AERs, pravastatin-associated RENAL FAILURE AERs, and atorvastatin-associated RENAL FAILURE AERs ($P < 0.001$ for each versus rosuvastatin; Figure 2G).

Secondary Analyses: First Year of Marketing

Figure 3 depicts the rates of AERs during the first postmarketing year for rosuvastatin compared with each of the other

statins during their first full year of marketing, as described in Methods. Compared with rates of ALL AERs associated with other statins in the first year of marketing analysis, the difference was less marked than with the concurrent time period analysis but was still significant. The rate of rosuvastatin-associated ALL AERs was higher than simvastatin, pravastatin, atorvastatin, and cerivastatin ($P < 0.001$ for each statin versus rosuvastatin; Figure 3A). For SERIOUS AERs, the rate for rosuvastatin-associated AERs was signif-

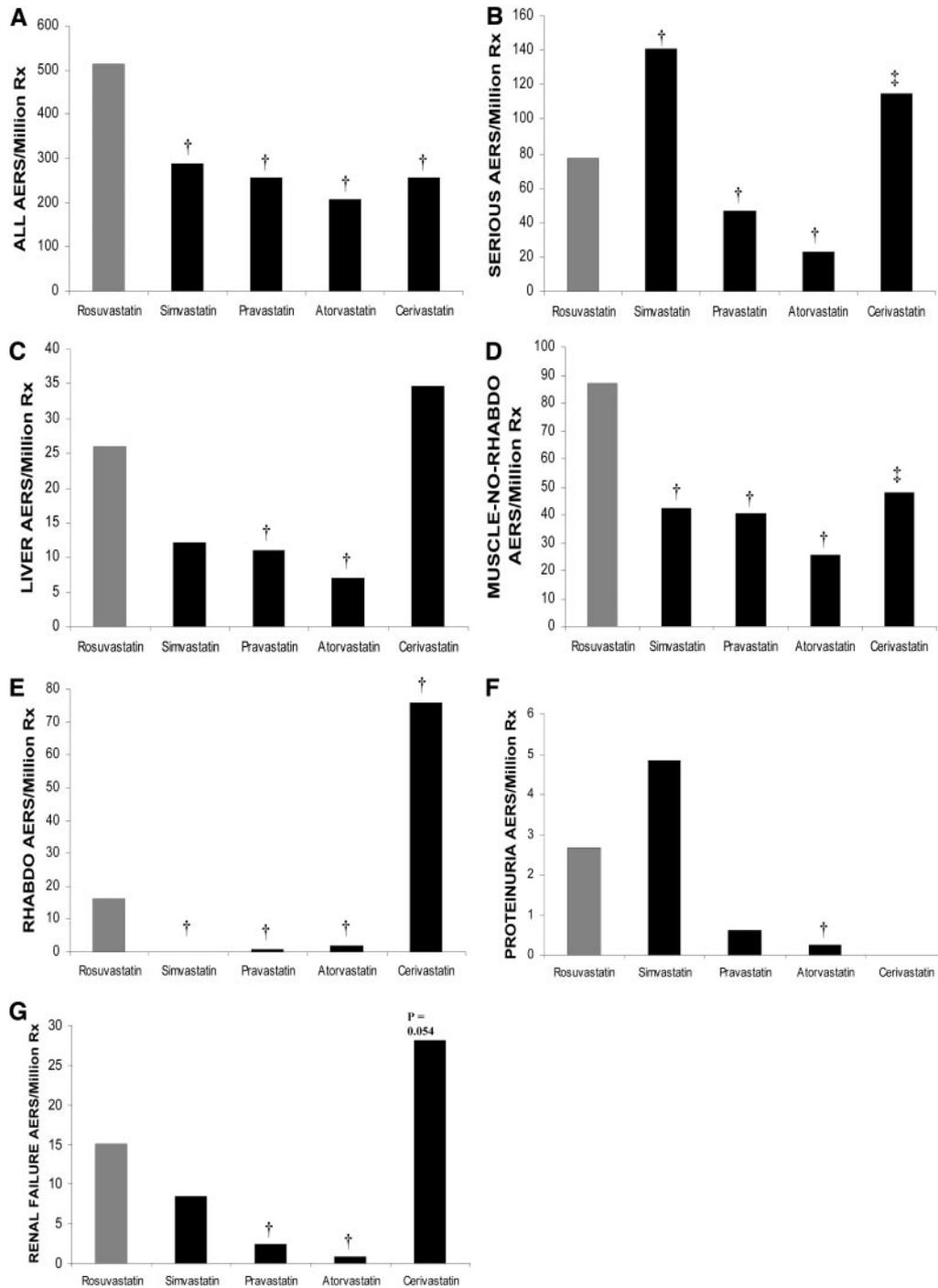


Figure 3. Rates of each category of AERs associated with various statins during respective first postmarketing year for each statin. A, ALL AERs; B, SERIOUS AERs; C, LIVER AERs; D, MUSCLE-NO-RHABDO AERs; E, RHABDO AERs; F, PROTEINURIA AERs; G, RENAL FAILURE AERs. All rates are per 1 million prescriptions (Rx). Note specific scale on vertical axis for each category of AERs. † $P < 0.001$, ‡ $P < 0.01$ for pairwise comparison vs rosuvastatin.

ificantly lower than simvastatin ($P < 0.001$) and cerivastatin ($P < 0.01$) but was significantly higher than what was observed with atorvastatin or pravastatin ($P < 0.001$ for both versus rosuvastatin; Figure 3B). For LIVER AERs, the rate for rosuvastatin was higher than what was observed with simvastatin, pravastatin, or atorvastatin ($P < 0.05$ for simvastatin versus rosuvastatin, $P < 0.001$ for pravastatin and atorvastatin versus rosuvastatin; Figure 3C) but was not signifi-

cantly different from what was observed with cerivastatin during its first postmarketing year (Figure 3C). The rate of rosuvastatin-associated MUSCLE-NO-RHABDO AERs was higher than what was observed with simvastatin, pravastatin, atorvastatin, and cerivastatin ($P < 0.001$ for simvastatin, pravastatin, and atorvastatin versus rosuvastatin; $P < 0.01$ for cerivastatin versus rosuvastatin; Figure 3D). Rosuvastatin was also significantly more likely than simvastatin, pravasta-

tin, and atorvastatin to be associated with reports of rhabdomyolysis ($P < 0.001$ for each statin versus rosuvastatin; Figure 3E). However, compared with the first year of cerivastatin, the rate of rosuvastatin-associated RHABDO AERs was significantly less ($P < 0.001$; Figure 3E). The rate of rosuvastatin-associated PROTEINURIA AERs was not significantly different from what was observed with simvastatin, pravastatin, and cerivastatin but was significantly higher than what was observed with atorvastatin ($P < 0.001$ for atorvastatin versus rosuvastatin; Figure 3F). Finally, the rate of rosuvastatin-associated RENAL FAILURE AERs was significantly greater than what was observed with pravastatin and atorvastatin ($P < 0.001$ for both versus rosuvastatin; Figure 3G) but was comparable to what was observed with simvastatin and tended to be lower than what was observed with cerivastatin ($P = 0.054$; Figure 3G).

Discussion

We reviewed rosuvastatin-associated adverse events reported to the US FDA over its first year of marketing and compared the rates of such events with other statins over the concurrent time frame and during their respective first year of marketing. We observed that with either comparison, rosuvastatin was several-fold more likely to be associated with the composite end point of rhabdomyolysis, proteinuria, nephropathy, or renal failure AERs. The increased rate of rosuvastatin-associated AERs relative to the 3 most widely used statins in the United States was also observed when other categories of AERs were examined, including serious adverse events and reports of liver toxicity, as well as muscle toxicity without rhabdomyolysis. There were a few exceptions in which this trend was not observed, such as the lower rate of serious AERs and a comparable rate of renal failure reports with rosuvastatin relative to the first year of marketing of simvastatin, as well as a relatively low incidence of proteinuria and nephropathy reports, comparable to what was observed during the first postmarketing year of simvastatin and pravastatin. We also observed that compared with first year of marketing of cerivastatin, the rate of rosuvastatin-associated liver injury reports was not significantly different.

The approach we used in the present analysis takes advantage of the “real-life” population exposure captured in the FDA AERs system. This overcomes the limitation of controlled premarketing trials, which typically exclude patients who may be predisposed to a certain adverse event but who nonetheless are likely to receive the drug after it is marketed. In addition, premarketing trials aimed at safety or efficacy assessment are often underpowered to detect relatively rare adverse events. Hence, postmarketing assessments such as the one presented here are helpful in attempts to identify safety concerns that can potentially be missed early on.

On the other hand, the findings we report should be interpreted within the context of the intrinsic limitations of postmarketing adverse event analyses. The data used reflect adverse event reporting rates, not actual adverse event rates. In clinical practice, adverse events tend to be underreported, and serious events are more likely to be reported than milder ones. Hence, the rates presented here are likely underesti-

mates of true adverse events with possible relative overrepresentation of serious events. Moreover, the retrospective nature of the analysis does not allow confirmation of causality or control of potential confounders.

One potential confounder is the time period studied relative to the life cycle of a drug, because providers tend to preferentially report adverse events associated with newly marketed drugs. In addition, certain adverse events may not be recognized as related to a particular class of drugs until later. For example, the very low rates of simvastatin- and pravastatin-associated RHABDO AERs during their first postmarketing year (1992) may be the result of underrecognition of this statin-related adverse event in an era predating the large landmark statin trials and the subsequent widespread use of these drugs. Postmarketing analyses can also be influenced by the publicity, favorable or otherwise, surrounding the drug of interest. Hence, it is conceivable that some of the negative publicity surrounding the safety profile of rosuvastatin and the accompanying heightened public awareness contributed to the increased rates of reported rosuvastatin-associated adverse events. The extent to which that publicity contributed to our findings is uncertain. Other time-dependent variables can potentially affect the assessment of postmarketing safety. For example, the relatively low rate of atorvastatin-associated AERs during its first year of marketing could be partially related to the availability of only the 10-mg dose during the first year, hence ameliorating the preferential reporting often seen early after the release of a new drug. Therefore, in an effort to account for possible time-dependent effects, we present comparisons of rosuvastatin-associated AERs during its first year of marketing with the other statins over the concurrent time frame and during the respective first year of marketing of each statin. Although the first year of marketing analysis is limited by the use of two different time points, it has the advantage of using similar phases of the life cycle of each drug.

An additional limitation of our findings is the lack of insight into the mechanism(s) that resulted in the higher rate of AERs with rosuvastatin. For example, it remains unclear whether the observed rate of rosuvastatin-associated AERs is due in part to its greater LDL-C-lowering effect compared with the other statins. If this were the case, then the rates of AERs with the other statins might also be higher if used at equivalent LDL-lowering doses. Despite this important caveat, however, our findings remain clinically relevant because they reflect the AERs observed with each statin as it is commonly used in clinical practice. Similarly, we are unable to provide insight about any potential role of the distinct chemical structure of each statin or of differences in metabolism or dose response.

In conclusion, this comparative postmarketing analysis of rosuvastatin-associated adverse events reported to the US FDA raises concerns about the safety of this drug at the range of doses used in common clinical practice in the general population. The occurrence of rhabdomyolysis and renal toxicity relatively early after initiation of therapy (within the first 12 weeks on average), suggests that vigilant surveillance for adverse effects during initiation of therapy may help ameliorate the risk of toxicity when rosuvastatin is used.

Healthcare providers and regulatory agencies will have to carefully consider the findings of this postmarketing analysis, along with safety analyses from clinical trials, to determine the extent to which the observed increased rates of AERs with rosuvastatin offset the potential benefit of its greater potency for LDL-C reduction. It would seem prudent at the current time for healthcare providers to consider other statins as first-line therapy, to initiate therapy in appropriate patients at lower doses, to consider combination LDL-C-lowering therapy (eg, statin combined with ezetimibe), and to vigilantly monitor for adverse events if rosuvastatin is used.

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Disclosure

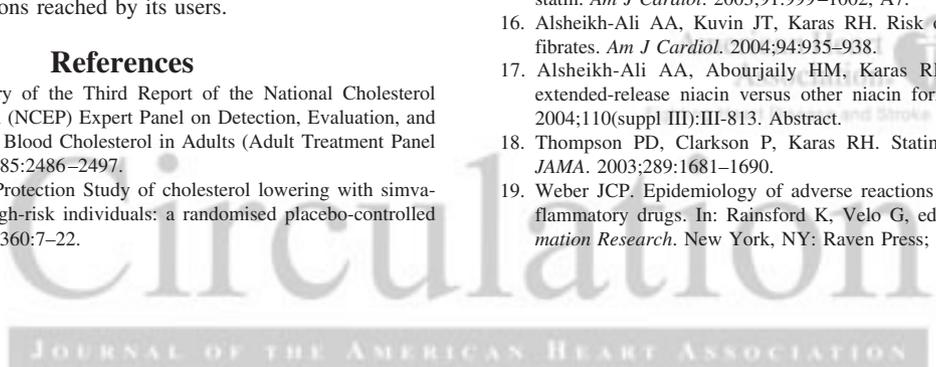
Dr Karas has received research grants from AstraZeneca and Kos Pharmaceuticals; has served on the Speakers' Bureaus of and/or received honoraria from Kos, AstraZeneca, Merck, and Pfizer; and has served as a consultant to Kos. Dr Kuvin has received research grants from AstraZeneca and has served on the Speakers' Bureaus of and/or received honoraria from Merck, Kos, and Pfizer.

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