

# Characteristics of Drug-Associated Rhabdomyolysis: Analysis of 8,610 Cases Reported to the U.S. Food and Drug Administration

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## Abstract

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**Objective** To describe the characteristics of cases with drug-associated rhabdomyolysis reported to the U.S. Food and Drug Administration (FDA).

**Methods** A retrospective analysis of all drug-associated rhabdomyolysis cases reported to FDA between January 2004 and December 2009 was conducted. The analyses included the number of unique cases, age, gender, body weight and proportion of fatal outcome. Time to onset from beginning of the suspected drugs and frequently reported suspected drugs were also tabulated.

**Results** There were 8,610 cases of drug-associated rhabdomyolysis in the database. Both case numbers and proportion of the fatal outcome appeared stable over the study period. Average age was 43.3 years old. The reported ratio of male to female was approximately 5 to 3. More than half of reported cases developed rhabdomyolysis within a month after beginning the suspected drug. Potential high risk groups for fatal outcome, such as age group younger than 10 years old and body weight group less than 50 kg were suggested. Suspected drugs for younger cases and their probable indication appear to be different from adult cases. There has been long standing controversial concern regarding an increased risk when a fibric acid derivative is added to an HMG-CoA reductase inhibitor. This study suggested that concomitant use of these two kinds of agents may be associated with a lower risk for fatal outcome, whereas renal dysfunction appeared to be associated with a higher risk for fatal outcome among the HMG-CoA reductase inhibitor-associated rhabdomyolysis cases.

**Conclusion** The characteristics of cases of drug-associated rhabdomyolysis were described. Because of the various limitations of a spontaneous reporting-system database, the reported number should be interpreted with caution.

**Key words:** adverse drug reaction, rhabdomyolysis, adverse event reporting system, epidemiology, FDA AERS, spontaneous report

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## Introduction

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Rhabdomyolysis is a potentially life-threatening syndrome, defined as necrosis of skeletal muscle and leakage of muscle-cell contents, including electrolytes, myoglobin, and other sarcoplasmic proteins. It is often caused by crush injuries to muscle, myocardial infarction, prolonged immobility, drug toxicities, hypothermia, and others (1, 2) Rhabdomy-

olysis is usually associated with symptoms such as muscle pain, weakness and brown urine, myoglobinuria, acute kidney injury, and markedly elevated creatine kinase levels. Acute kidney injury in myoglobinuria is caused by tubular injury resulting from excessive quantities of myoglobin. The incidence of rhabdomyolysis is difficult to establish owing to varying definitions and clinical scenarios. Moreover, since the rhabdomyolysis is a relatively rare condition, the rate of rhabdomyolysis in the general population is difficult to es-

establish with certainty, but it was estimated to be about 1-2 cases per 10,000 person-years for HMG-CoA reductase inhibitor-associated and HMG-CoA reductase inhibitor-independent rhabdomyolysis (3). It is generally considered that the earlier diagnosis and treatment of rhabdomyolysis may be associated with a better outcome. Sufficient knowledge of rhabdomyolysis is essential for early detection of signals of rhabdomyolysis. The reported characteristics of patients are limited. Moreover, the reported characteristics vary widely according to the study population and severity of coexisting conditions. For example, mortality was reported to range from 3.4% to 32% among patients with rhabdomyolysis (4).

In this study, I describe the characteristics of drug-associated rhabdomyolysis reported to the U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (AERS). The FDA-AERS is a computerized information database designed to support the FDA's post-marketing safety surveillance program for all approved drug and therapeutic biologic products. Adverse drug reaction (ADR) reports have been entered into the AERS database since 1997 by drug and event. The drug manufacturers are required to report ADR associated with their drug products to FDA. FDA also receives ADR directly from health care professionals including physicians, pharmacists, and patients who were treated with the suspected drug. FDA allows the downloading the various data extracted from AERS database. The data currently contains more than 2.0 million ADR cases. Of the approximately 490,000 reports the FDA received and entered into the database in 2009. The FDA-AERS data do have some limitations. First of all, there is no certainty that the reported event was actually due to the product. Even though each provided individual case was reviewed by specialists, the causality assessment for each case is preliminary judgment and is only for regulatory purpose. Detailed causality assessment between reported ADR and the product will be done by reviewing aggregated reports later. Another limitation is that only a portion of all ADRs are reported to the FDA, which is called "underreporting". Since the exact number of population who are exposed to the drugs is not known, the incidence of the ADR associated with the drug cannot be calculated. The fraction of reports received by the FDA has been estimated to be 1% to 10%, but the absolute percentage is unknown (5). In addition to the underreporting, since the report is highly dependent on spontaneous reports, there are many potential factors which may affect reporting. If errors occur randomly, the errors will reduce the potential signal and will be considered noise. Since the spontaneous report is made under less strict conditions than a clinical study, there may be chances for simple error. This kind of error usually results in noise. If the factor has an affect to mislead the results towards a specific direction, the factor may be called bias. For example, if the ADR is serious, physicians may want to report the ADR. This could make the cases in database shift to more serious events. In spite of underreporting, noise and potential bias in the

AERS database, since the AERS is the biggest source of ADR, many approaches have been taken to use the AERS in quantitative epidemiologic studies and hypotheses creation in drug safety studies (6-10). The data may allow me to describe the characteristics of drug-associated rhabdomyolysis based on analysis of the AERS.

## Methods

### DATA source

The AERS database was downloaded from FDA AERS web page (<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/>). Since FDA allows AERS data to be downloaded from their web page between 2004 Q1 and 2009 Q4 at the time of beginning of this study, I analyzed AERS data from during this period. The US demographic statistics were downloaded from the Census Bureau of USA (<http://www.census.gov/>). The population posted on the web page is expressed as the number of residents on July 1 of each year. For this tabulation the estimated population was regarded as person-year for each year and was used as the denominator for each corresponding age group. Since Census Bureau posted statistics until 2008 at the web page, and AERS harbors reporting country information since 2005 Q3, analysis using demographic statistics of US population was limited to between 2006 and 2008.

### Case identification

Reports of rhabdomyolysis associated with any drug use were obtained from AERS database. Since reported ADR in AERS database are coded according to Medical Dictionary for Regulatory Activities (MedDRA) ([http://www.meddrasso.com/public\\_about\\_meddra.asp](http://www.meddrasso.com/public_about_meddra.asp) MedDRA MSSO3975 Virginia Mallory Drive Chantilly, VA 20151 USA), I identified rhabdomyolysis cases by preferred term (PT) coded as "rhabdomyolysis". There were 12,862 reports of rhabdomyolysis between 2004 and 2009. Duplicate reports are reports regarding the same case but the information in the reports is generally not identical. Usually a follow-up report with more detailed information or with longer term outcome is reported after the initial report. Since the AERS database has some duplicate reports, I removed the older one from duplicate reports by sorting by case identification number. After the removal of the duplicate report, there were 8,610 reports of rhabdomyolysis. The 8,610 reports were placed in further analysis. I used SMQ (Standardized MedDRA Queries; [http://www.meddrasso.com/public\\_about\\_meddra.asp](http://www.meddrasso.com/public_about_meddra.asp) MSSO3975 Virginia Mallory Drive Chantilly, VA 20151 USA) code 20000003 to identify decline in renal function. The PT terms corresponding code 20000003 within the REAC table of FDA AERS were searched. This procedure was supposed to search for a relatively rapid decline in renal function that lead to any of following: the accumulation of water, crystalloid solutes, nitrogenous metabolites in the

body, increase in serum creatinine and urea nitrogen levels (azotemia) greater than 0.5 and 10 mg per deciliter, respectively; oliguria; and changes in the rate of urine flow. Out of 2,523 HMG-CoA reductase inhibitor-associated rhabdomyolysis case, 996 cases (39.5%) were identified coexistence of renal dysfunction. The renal dysfunction search was intended to search for *de novo* onset in individuals whose baseline renal function was within normal limits and acute exacerbation of pre-existing chronic renal insufficiency.

### Analysis

The identified reports were tabulated by reporting year, gender, age, body weight, and suspected drugs. Reporting year is calculated from reporting date (FDA\_DT in the database) that is the date FDA received the report. Gender is calculated from gender code (GNDR\_COD in the database). Age is calculated from age (AGE in the database) that is numeric value of patient's age at event. In this study, I converted all age in "years old" unit if the reported age is not in years old. Similarly, body weight is calculated from weight (WT in the database). If the unit was LBS (pounds), the numeric value was converted in kilograms by multiplying by 0.45359237. The suspected drugs are tabulated from DRUG data. It harbors not only suspected drugs but also concomitant drugs. In this study I tabulated only for suspected drugs. The duration between the beginning of medication and event onset was also tabulated. Since some information is missing, the number of reported cases is diverse between tabulations. DRUG data are first converted into substance name. In this study, terms used to search HMG-CoA reductase inhibitors were as follows: simvastatin, atorvastatin, rosuvastatin, pravastatin, fluvastatin, losuvastatin, cerivastatin and pitavastatin. Similarly, terms for searching fibric acid derivatives included gemfibrozil, fenofibrate, bezafibrate and ciprofibrate.

### Software

Microsoft Access 2003 (Microsoft Corporation, Redmond WA, USA) was used for data management and analyses. Analyses of 95% confidence interval of death proportion were performed using CDC EpiInfo software (the Centers for Disease Control and Prevention (CDC), Atlanta GA, USA).

## Results and Discussion

As mentioned above, there were 8,610 cases reported as rhabdomyolysis. Among the 8,610 cases, 927 (10.8%) indicated fatal outcome. As a potential cause of the reported events, 16,435 suspected drugs were identified in the database.

Trend of reporting number and fatality of rhabdomyolysis cases are shown by reporting the year in Fig. 1. The reporting in each year was between 1,280 and 1,569 cases (upper panel of Fig. 1). The proportion of fatal outcome in rhabdomyolysis was between 9.2% and 12.9% (lower panel of

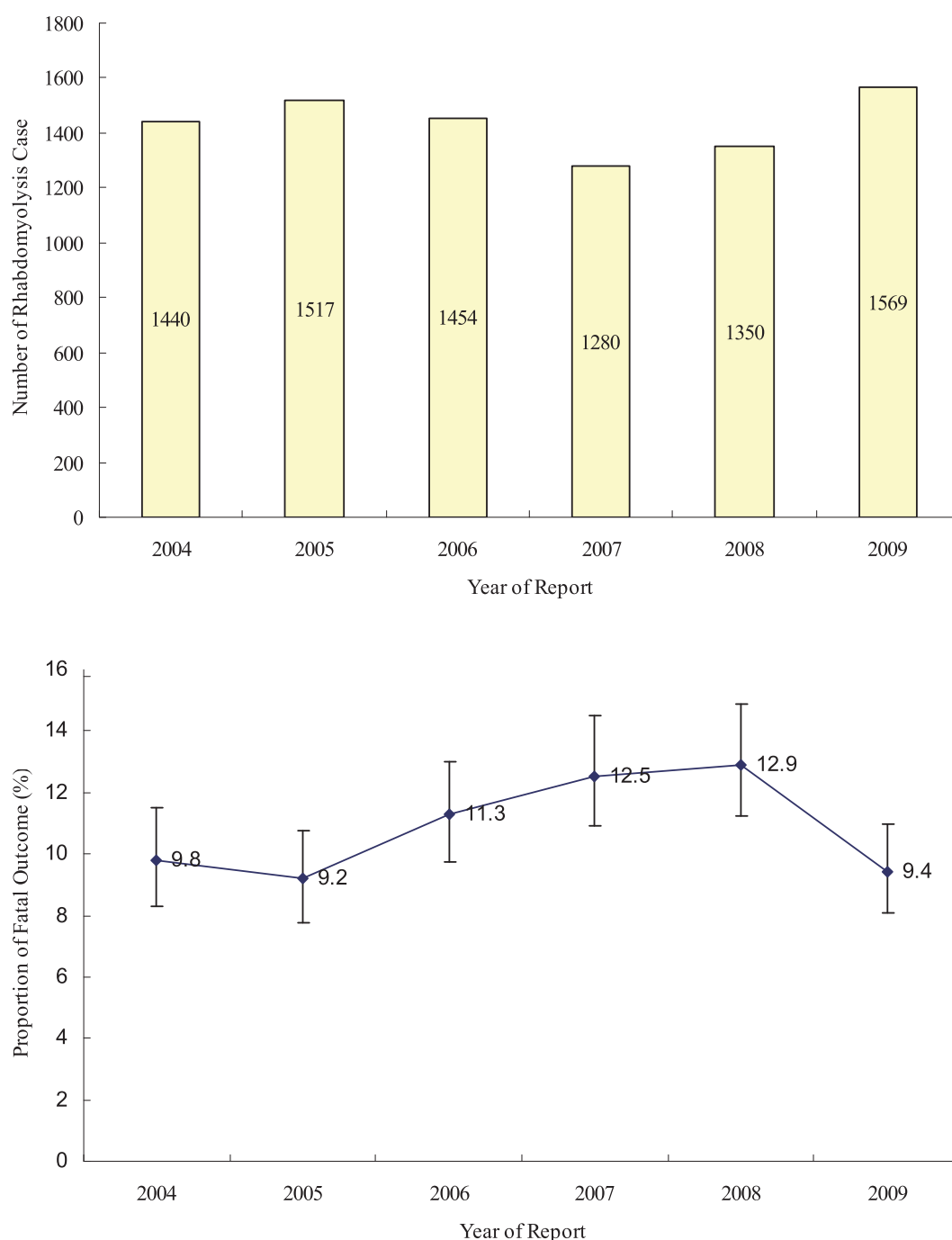
Fig. 1). There appears to be no meaningful tendency in both the reporting number and its fatal outcome proportion over the study period.

The reported case numbers for males and females were 4889 and 3036, respectively. The absolute case number in this observation study and odd ratio in a past case-control study should not be compared directly, but it has been previously reported that females were not significant but a higher odds ratio for HMG-CoA reductase inhibitor-associated rhabdomyolysis (11). In the past case series report, only 21 HMG-CoA reductase inhibitor-associated rhabdomyolysis cases were analyzed. Thus, the power of demographics description in the past report may be limited. Despite the limitations of spontaneous ADR reporting, the difference of reporting in this database may reflect real facts to some extent. Since the drug-exposed population is not known, the incidence was not calculated. The difference of rhabdomyolysis reports among gender groups could be due to the difference of drug-exposed population number. And it also may possibly reflect the incidence of gender difference of rhabdomyolysis. The proportion of fatal outcome for males and females were 11.8% and 10.6%, respectively. The odds ratio for fatal outcome in females compared to males was 1.12 (95% CI: 0.97-1.30). The p-value calculated with Fisher's exact test was 0.121. Thus, the proportion of fatal outcome in both genders appeared to be similar.

The reporting number and fatality of rhabdomyolysis as categorized by age group are shown in Fig. 2. For cases less than 80 years old, older age appears to be associated with a higher number of reporting. This trend appears to be similar if the reporting number is expressed in person-year in USA. The reporting rate was from 0.1 to 5.2 per million person-year as shown in upper panel of Fig. 2. In the present study, the proportion of fatal outcome in cases aged between 80 and 89 did not appear to exceed the outcome of those aged between 10 and 79 (Fig. 2). In contrast, for cases younger than 10 years old, fatality appears to be higher if compared to those between 20 and 89. The odds ratio for fatal outcome in this age group compared to the other age group was 3.09 (95% CI; 1.94-4.91). The p-value calculated with Fisher's exact test was less than 0.0001. Thus it is suggested that the reporting number of cases younger than 10 years old may be low, but once the rhabdomyolysis developed the fatality may be relatively higher in this age group.

The reporting number and fatality of rhabdomyolysis in adults categorized by body weight group are shown in Fig. 3. Since the younger age appears to be confounded with body weight, cases less than 20 years old were removed from this analysis. The reporting number was the highest in the weight group between 70 and 79 kg. The fatality appears to be higher in cases with a weight of less than 50 kg.

Table 1 shows the 46 most frequently reported suspected drugs and the number of reports. Consistent with previous reports, lipid modifying agents, such as HMG-CoA reductase inhibitors were most frequently reported as a suspected

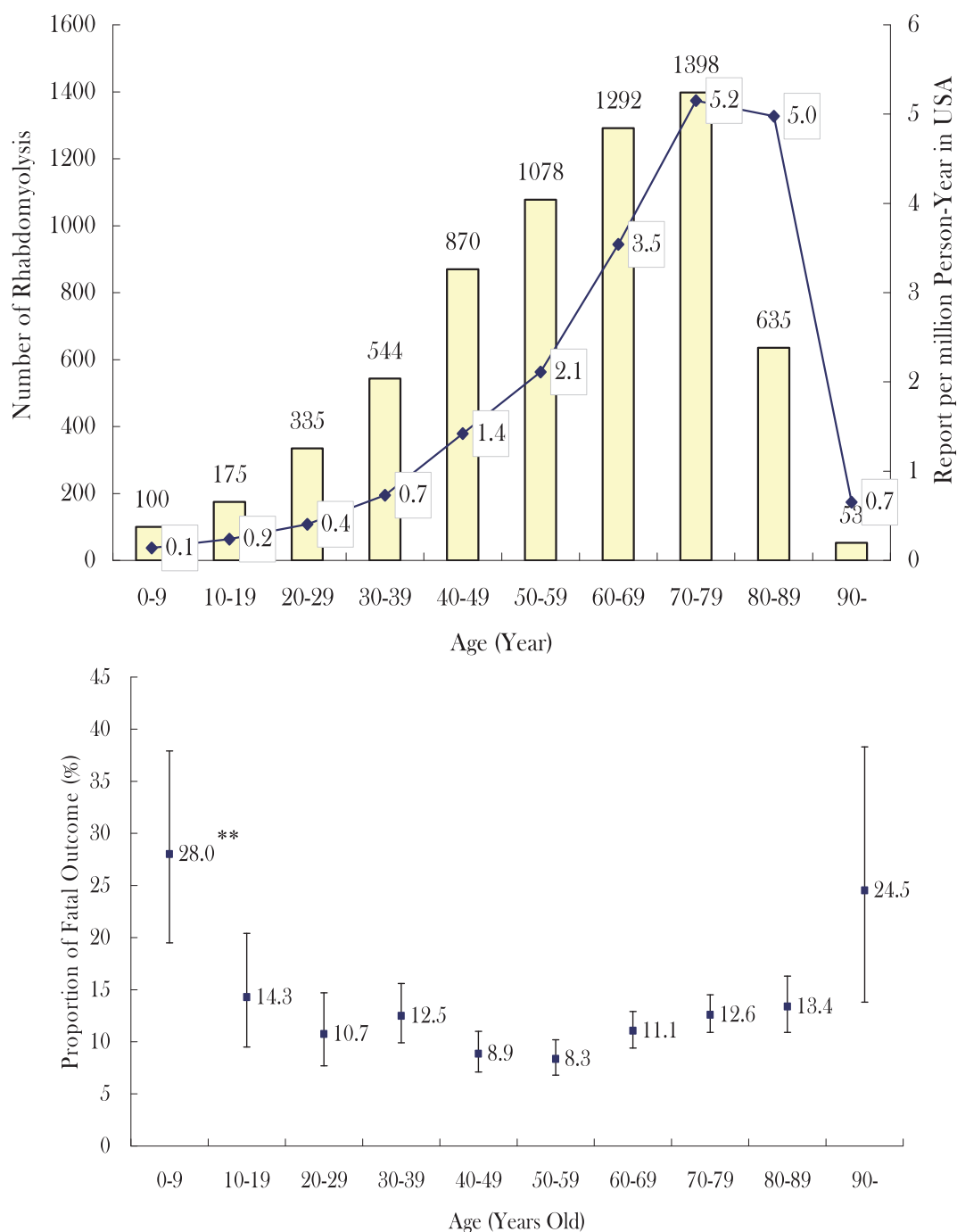


**Figure 1.** Reporting of rhabdomyolysis cases to AERS between 2004 and 2009. Upper panel indicates the annual number of rhabdomyolysis case reported to AERS between 2004 and 2009. Lower panel indicates the proportion of fatal outcome (%) of the reported rhabdomyolysis cases to AERS. Error bars indicate 95% confidence intervals.

cause of reported rhabdomyolysis (1, 12). Since the HMG-CoA reductase inhibitors are usually used in treatment of hyperlipidemia, which is well known to occur in adults, I also analyzed most frequently reported drugs in the younger age group. As shown in Table 2, there were 123 suspected drugs reported in 100 rhabdomyolysis cases younger than 10 years old. No HMG-CoA reductase inhibitors were reported as a suspected drug. Instead, anesthetic agents, hemophilia therapeutic agents, antifungal agents, immunosuppressants and so on were listed. This indicates the underlying diseases

of younger age group appeared to be quite different from those of adults. This may at least in part explain the higher fatal outcome proportion in this age group.

The mean daily dose for HMG-CoA reductase inhibitors, except for simvastatin, did not exceed the maximum daily dose in US prescribing information (Table 3). Thus most HMG-CoA reductase inhibitor-treated cases might not be due to overdosing. Though, the mean daily dose for fluvastatin, pravastatin and simvastatin were higher than the maximum daily dose in the Japan prescribing information.

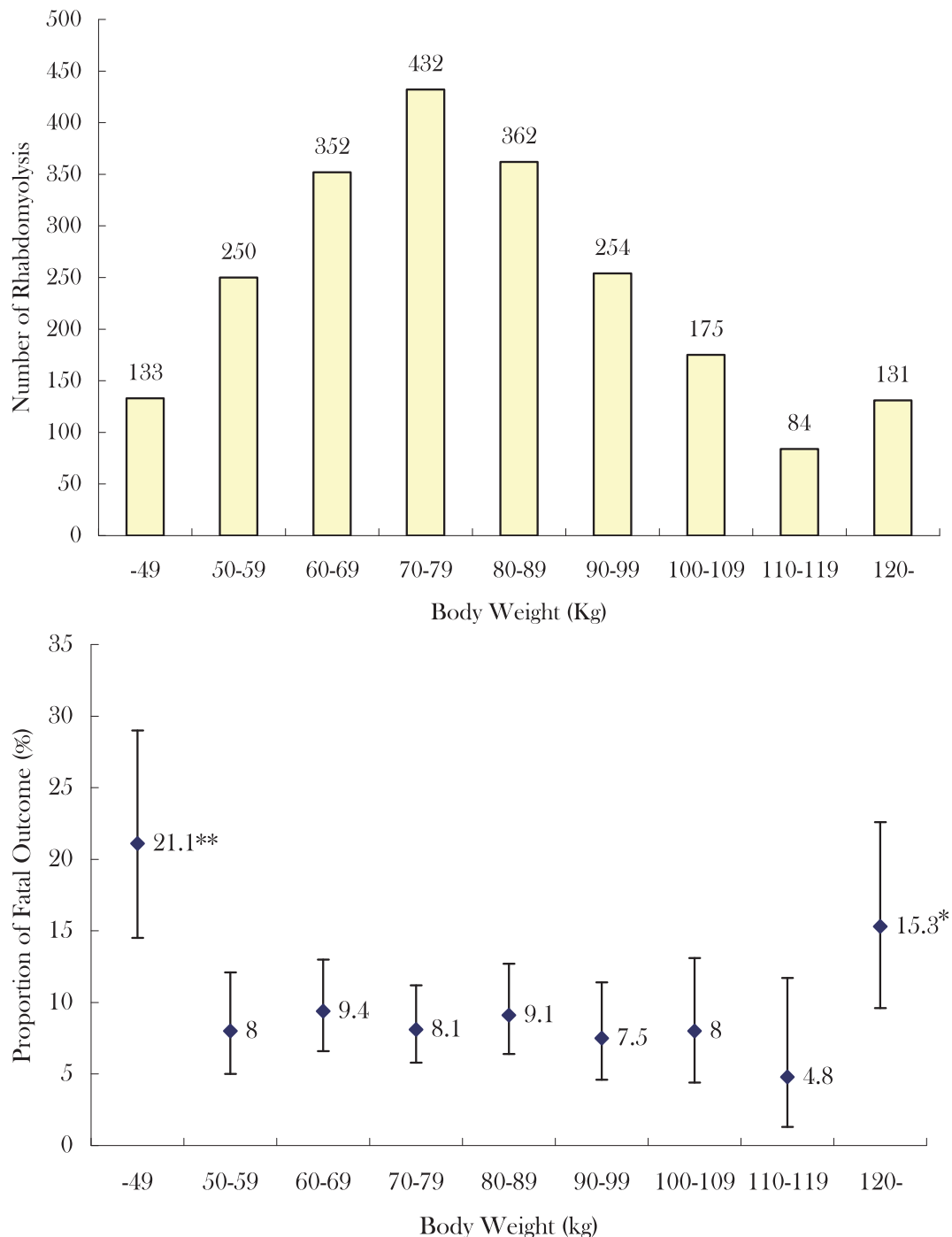


**Figure 2.** Reporting of rhabdomyolysis cases to AERS classified by age group. Bars and line plots in the upper panel indicate the number of rhabdomyolysis cases and the reporting rate per million of person-years by age group reported to AERS. The denominators for reporting rate were estimated based on population of US residents. Lower panel indicates proportion of fatal outcome (%) of the reported rhabdomyolysis cases to AERS. Error bars indicate 95% confidence intervals. (\*\*The odds ratio for fatal outcome in 0-9 age group compared to other age group was 3.09 (95% CI; 1.94-4.91). p-value calculated with Fisher's exact test was less than 0.0001.)

Duration from beginning of suspected medication to the reported event onset (time to onset) is shown in Fig. 4. Due to missing data, only a part (7,042 out of 16,435 suspected drugs) of 8,610 cases had a relevant date for beginning of medication and event onset date. Approximately 44.4% of reported cases of rhabdomyolysis occurred within a month after beginning of suspected drugs and up to 1,000 days

from beginning of medication, approximately 90% of reported cases developed rhabdomyolysis.

Gemfibrozil was reported to increase the risk of rhabdomyolysis with HMG-CoA reductase inhibitors especially in patients with renal dysfunction (13-15). According to a doctor's letter released in December 1999, cerivastatin and gemfibrozil (another cholesterol-lowering drug) should never be



**Figure 3.** Reporting of adult rhabdomyolysis cases to AERS by body weight. Upper panel indicates the number of rhabdomyolysis cases according to body weight (kg) group reported to AERS. Lower panel indicates the proportion of fatal outcome (%) of the rhabdomyolysis cases reported to AERS. Error bars indicate 95% confidence intervals. (\*\*The odds ratio for fatal outcome in <50 kg body weight group compared to the other group was 2.79 (95%CI; 1.74-4.44). p-value calculated with Fisher's exact test was less than 0.0001. \*Similarly, the odds ratio for fatal outcome in the weight group 120kg or more was 1.80 (95%CI; 1.06-3.03), with p-value 0.020.)

used in combination due to the increased risk of a serious side effect, rhabdomyolysis. Then other HMG-CoA reductase inhibitors followed this safety communication. However, a recent open-label placebo controlled trial did not indicate such evidence for the increased risk for rhabdomyolysis when a fibric acid derivative is added to an HMG-CoA reductase inhibitor (16). I analyzed regarding the concomi-

tant use of HMG-CoA reductase inhibitors and fibric acid derivatives. In the previous report, one hundred and twenty-five cases (67.6%) out of 185 cerivastatin-associated rhabdomyolysis cases reported to AERS were prescribed concomitant gemfibrozil between September 1999 and July 2000 (17, 18). On the other hand, only 220 cases (8.7%) out of 2,523 HMG-CoA reductase inhibitor-associated rhabdo-



**Table 1. Frequently Reported Suspected Drugs in Rhabdomyolysis Cases to AERS**

Suspected Drug	Number of Report	Suspected Drug	Number of Report
simvastatin	2164	losartan	99
atorvastatin	1039	omeprazole	99
rosuvastatin	742	candesartan	94
ezetimibe	647	amlodipine	89
gemfibrozil	285	lamotrigine	86
risperidone	257	paroxetine	85
propofol	254	fluconazole	83
ciclosporin	220	sertraline	77
olanzapine	214	clonidine	76
fenofibrate	212	levofloxacin	76
quetiapine	165	diltiazem	75
clarithromycin	148	rofecoxib	74
pravastatin	148	fentanyl	73
fluvastatin	118	pregabalin	72
lovastatin	114	metformin	71
clozapine	113	morphine	71
furosemide	112	donepezil	70
amiodarone	107	aripiprazole	69
valproate	106	ciprofloxacin	68
haloperidol	104	amoxicillin	66
paracetamol	103	nicotinic	62
venlafaxine	101	insulin	61
diclofenac	100	ramipril	61

This table shows the top 46 frequently suspected drugs. Since some cases were reported along with more than one suspected drug. There are 16,435 suspected drugs.

**Table 2. Suspected Drugs in Rhabdomyolysis Cases Younger than 10 Years Old**

Suspected Drug	Number of Report
propofol*	12
desmopressin acetate	8
rocuronium bromide	6
azithromycin	4
filgrastim	4
amphotericin b	3
calcium carbonate	3
eptacog alfa (activated)*	3
itraconazole	3
mycophenolate mofetil	3
paracetamol	3
atomoxetine hydrochloride	2
caffeine	2
carbamazepine	2
cefaclor*	2
cefdinir	2
chorionic gonadotrophin*	2
clarithromycin	2
fluticasone propionate*	2
ganciclovir	2
montelukast	2
oseltamivir phosphate	2
tacrolimus	2
vecuronium bromide	2

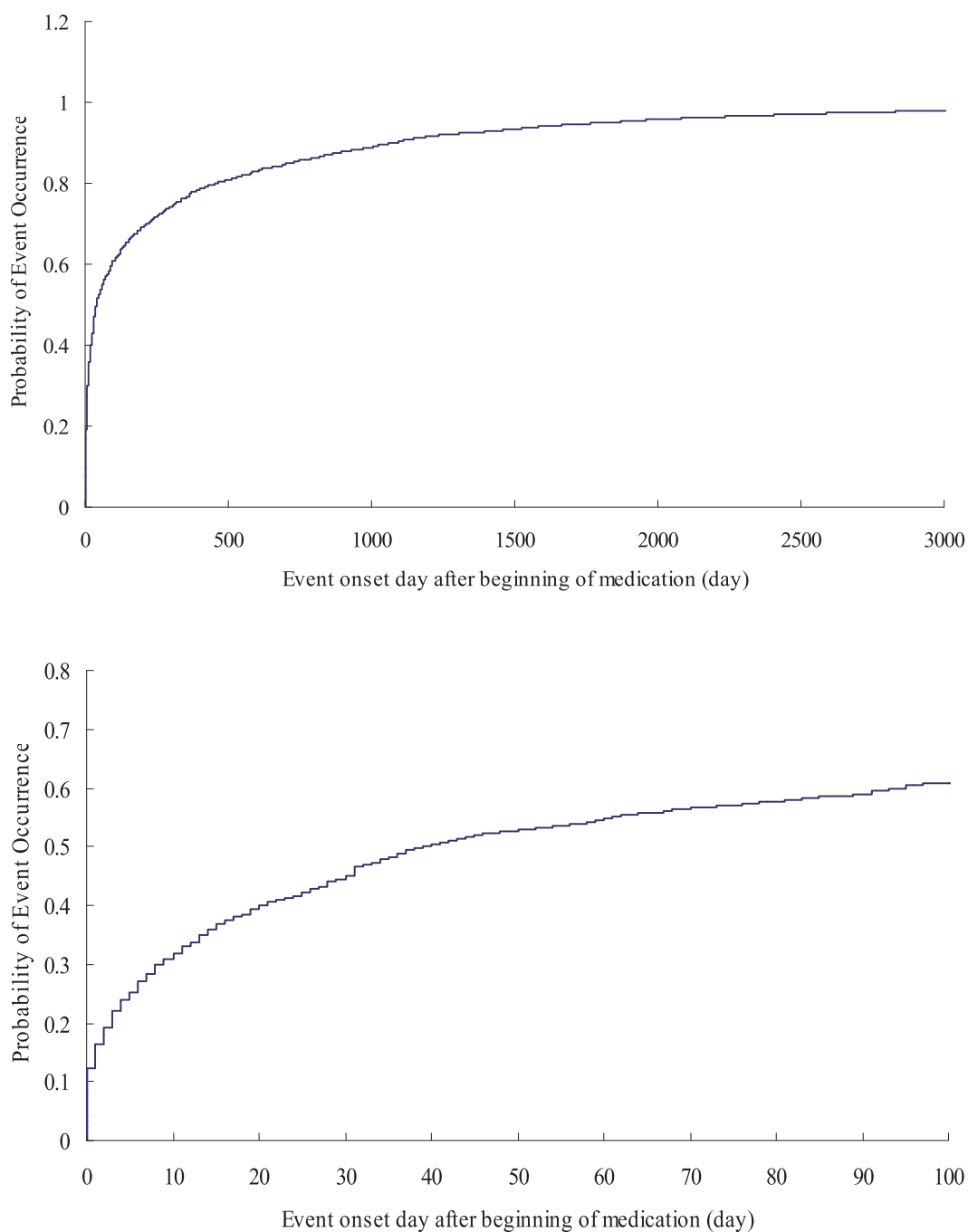
This table shows suspected drugs reported more than once. There were 123 suspected drugs in 100 rhabdomyolysis cases younger than 10 years old. Drugs reported with fatal outcome are marked with (\*).

letter and prescribing information. Proportion of fatal outcome for HMG-CoA reductase inhibitor-associated rhabdomyolysis case with or without concomitant fibric acid derivatives were 5.5% (95% CI, 2.8-9.3) and 9.7% (95% CI, 8.5-11.0), respectively. Thus, the proportion for fatal outcome appeared to be lower in fibric acid derivatives co-treated subjects. The odds ratio for fatal outcome was 0.54 (95% CI; 0.28-1.01). The p-value calculated using Fisher's exact test was 0.0392.

Renal insufficiency is also reported to the risk of rhabdomyolysis with HMG-CoA reductase inhibitors (19). As mentioned before, 2,523 cases out of 8,610 rhabdomyolysis case were treated with HMG-CoA reductase inhibitors. Out of 2,523 cases, 996 case (39.5%) were reported coexistence of renal dysfunction. The proportion for fatal outcome in with or without coexistence of renal dysfunction were 13.5% (95% CI; 11.4-15.8) and 6.6 % (95% CI; 5.4-8.0), respectively. The odds ratio for fatal outcome was 2.19 (95% CI; 1.66-2.91). P-value calculated with Fisher's exact test was less than 0.0001.) Thus, coexistence of renal dysfunction among the HMG-CoA reductase inhibitor-associated rhabdomyolysis cases appeared to be associated with a higher proportion of fatal outcome.

As mentioned above, there were 220 cases co-treated with both HMG-CoA reductase inhibitors and fibric acid derivatives. There were 114 and 106 cases among the 220 co-treated cases with and without renal dysfunction, respectively. The proportion for fatal outcome with or without coexistence of renal dysfunction was 10.5% (95% CI; 5.6-17.7) and 0.0% (95% CI; 0.0-3.4), respectively. The odds ratio for fatal outcome was 0.00 (95% CI; 0.00-0.43). P-

myolysis cases were prescribed concomitant fibric acid derivatives between January 2004 and December 2009. This reduced proportion of concomitant use may be due to the successful communication from regulatory health authorities and market authorization holders including the dear doctor's



**Figure 4.** Event onset after beginning of suspected drug (n=7,042). Upper panel is Kaplan-Meier plot indicating time to event onset of rhabdomyolysis cases reported to AERS. Lower panel shows magnified view of the upper panel for onset day between 0 and 100. Approximately 44.4% of reported cases developed rhabdomyolysis within a month after beginning of suspected drug and up to 1000 days after beginning of suspected drug, approximately 90% of reported cases developed the event.

values calculated using Fisher's exact test was 0.0006. Thus, the absence of renal dysfunction appears to be associated with the lower proportion of fatal outcome in the co-treated cases.

### Conclusion

The characteristics of drug-associated rhabdomyolysis were evaluated by analyzing FDA AERS database. Potential high risk groups for fatal outcome, such as age group

younger than 10 years old and body weight group of less than 50 kg are suggested. In addition to low body weight, a previously known risk factor, the underlying diseases in younger cases appeared to be different from those of adults. There has been a long-standing controversial concern regarding an increased risk for rhabdomyolysis when a fibric acid derivative is added to an HMG-CoA reductase inhibitor. The present data suggest that there was a much lower proportion of concomitant use of these substances compared to an earlier report. Moreover, concomitant use of these two



**Table 3. Daily Dose of HMG-CoA Reductase Inhibitors**

	Mean (mg)	SD	daily dose (mg) in Japan PI		daily dose (mg) in US PI	
			recommended	maximum	recommended	maximum
atorvastatin	28.4	25.9	10	40	10 - 20	80
cerivastatin	0.49	0.21	-	-	-	-
fluvastatin	60.5	29.3	20 - 30	60	20 - 80	80
pitavastatin	1.67	0.58	1 - 2	4	1 - 4	4
lovastatin	58.9	40.2	-	-	-	-
pravastatin	29	17.1	10	20	40	80
rosuvastatin	17.6	12.1	2.5 - 5	20	10 - 20	40
simvastatin	56.6	43.4	5	20	20 - 40	40

Mean and standard deviation (SD) of daily dose of HMG-CoA reductase inhibitors are indicated for rhabdomyolysis cases reported to FDA AERS. Their daily dose, except cerivastatin and lovastatin, labeled in Japan and US prescribing information (PI) as of October 2010 is also shown.

kinds of agents appeared to be associated with a lower proportion of fatal outcome. Due to the following limitations, the suggested potential risk is only a signal of real risk of the fatal outcome. Further investigations are needed to determine whether the signal is real risk or not.

### Limitations

As the nature of a spontaneous report, there are some limitations such as lack of a denominator. Since there is no information regarding the drug-exposed population, no incidence of ADR can be calculated. Other limitations are as follows; lack of research protocol, and duplicated case reports. Due to the lack of a research protocol, ADR reports are not systematically collected. This usually results in underreporting. There may be reporting bias and noise of information; it also may fail to collect possible confounding factors. Moreover, there is no certainty whether a reported event was actually the result of the suspected products or not.

### Author's disclosure of potential Conflicts of Interest (COI).

Oshima Y: Employment, Sanofi-Aventis kk.

### References

- Harrison's Principles of Internal Medicine. Fauci AS, Kasper DL, Longo DL, Eds. McGraw-Hill, New York, 2008.
- Current Medical Diagnosis & Treatment. 49th ed. McPhee SJ, Papadakis MA, Eds. McGraw-Hill, New York, 2010.
- Nichols GA, Koro CE. Does statin therapy initiation increase the risk for myopathy? An observational study of 32,225 diabetic and nondiabetic patients. *Clin Ther* **29**: 1761-1770, 2007.
- Bosch X, Poch E, Grau JM. Rhabdomyolysis and acute kidney injury. *N Engl J Med* **361**: 62-72, 2009.
- Brinker A, Beitz J. Use of a spontaneous adverse drug events database for identification of unanticipated drug benefits. *Clin Pharmacol Ther* **71**: 99-102, 2002.
- Bennett CL, Nebeker JR, Lyons EA, et al. The research on adverse drug events and reports (RADAR) project. *JAMA* **293**: 2131-2140, 2005.
- Bennett CL, Nebeker JR, Yarnold PR, et al. Evaluation of serious adverse drug reactions: a proactive pharmacovigilance program (RADAR) vs safety activities conducted by the food and drug administration and pharmaceutical manufacturers. *Arch Intern Med* **167**: 1041-1049, 2007.
- Cope JU, Morrison AE, Samuels-Reid J. Adolescent use of insulin and patient-controlled analgesia pump technology: a 10-year food and drug administration retrospective study of adverse events. *Pediatrics* **121**: e1133-e1138, 2008.
- Fernandez AB, Karas RH, Alsheikh-Ali AA, Thompson PD. Statins and interstitial lung disease: a systematic review of the literature and of food and drug administration adverse event reports. *Chest* **134**: 824-830, 2008.
- Moore TJ, Cohen MR, Furberg CD. Serious adverse drug events reported to the food and drug administration, 1998-2005. *Arch Intern Med* **167**: 1752-1759, 2007.
- Schech S, Graham D, Staffa J, et al. Risk factors for statin-associated rhabdomyolysis. *Pharmacoepidemiol Drug Saf* **16**: 352-358, 2007.
- Omar MA, Wilson JP. FDA adverse event reports on statin-associated rhabdomyolysis. *Ann Pharmacother* **36**: 288-295, 2002.
- Pierce LR, Wysowski DK, Gross TP. Myopathy and rhabdomyolysis associated with lovastatin-gemfibrozil combination therapy. *JAMA* **264**: 71-75, 1990.
- Shek A, Ferrill MJ. Statin-fibrate combination therapy. *Ann Pharmacother* **35**: 908-917, 2001.
- Jones PH, Davidson MH. Reporting rate of rhabdomyolysis with fenofibrate + statin versus gemfibrozil + any statin. *Am J Cardiol* **95**: 120-122, 2005.
- Ginsberg HN, Elam MB, Lovato LC, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med* **362**: 1563-1574, 2010.
- Psaty BM, Furberg CD, Ray WA, Weiss NS. Potential for conflict of interest in the evaluation of suspected adverse drug reactions: use of cerivastatin and risk of rhabdomyolysis. *JAMA* **292**: 2622-2631, 2004.
- Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. *JAMA* **289**: 1681-1690, 2003.
- Pasternak RC, Smith SC Jr, Bairey-Merz CN, Grundy SM, Cleeman JJ, Lenfant C. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *Stroke* **33**: 2337-2341, 2002.