compelling data to support potassium levels above 4.5 mEq/L in patients with AMI, we believe the guidelines should be adjusted, pending additional studies examining potassium targets and potassium-modifying therapies in patients with AMI. 

Abhinav Goyal, MD, MHS
John A. Spertus, MD, MPH
Mikhail Kosiborod, MD

Author Affiliations: Department of Medicine, Emory School of Medicine, Atlanta, Georgia (Dr Goyal); and St Luke’s Mid America Heart Institute, Kansas City, Missouri (Dr Spertus and Kosiborod). 

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In Reply: Dr Robey highlights the challenges of interpreting population-based research and the need to individualize the treatment of hypokalemia or hyperkalemia based on the patient’s underlying pathophysiology. Current practice guidelines1 based on small, observational studies recommend maintenance of normal potassium levels, in particular among patients with significant ventricular ectopy. Despite a lack of compelling clinical data, many hospitals routinely implement automated algorithms for potassium supplementation that target potassium levels above 3.5 or 4.0 mEq/L in a broad range of hospitalized patients, including those presenting with AMI. Thus, the widespread assumption that routine potassium repletion is medically necessary persists, and achieving these targets requires significant resources. The report by Goyal et al2 is one of the largest studies to evaluate the relationship between potassium level and outcomes in AMI. Despite the inherent limitations of any observational, population-based study, the findings from Goyal et al are a substantial step forward from the previous small reports and should remind clinicians of the value of reevaluating habitual clinical practices based on sparse data.

Benjamin M. Scirica, MD, MPH
David A. Morrow, MD, MPH

Author Affiliations: Cardiovascular Division, Brigham and Women’s Hospital, Boston, Massachusetts (bscirica@partners.org).

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Use of Administrative Data to Estimate the Incidence of Statin-Related Rhabdomyolysis

To the Editor: Studies of rare adverse drug reactions (ADRs) are difficult because they require large numbers of exposed persons to identify an adequate number of cases. Spontaneous adverse events reports have been used to identify cases of rhabdomyolysis, a rare but serious complication of statin use.1 A complex algorithm based on administrative data also has been used to identify cases of rhabdomyolysis and myopathy among enrollees of several large health plans.2,3 We conducted this population-based epidemiological study to evaluate use of the diagnostic code for rhabdomyolysis introduced in 2006 as a method of estimating the incidence of statin-related rhabdomyolysis and myopathy.

Methods. Computerized pharmacy data were used to estimate the total person-years of statin use by statin type and dose among all enrollees of Group Health Cooperative (GHC) from January 2006 through December 2010. Trained abstractors reviewed the full electronic medical record (EMR) of all GHC enrollees who (1) had a statin prescription within 3 months before an outpatient or inpatient encounter with an International Classification of Diseases, Ninth Revision (ICD-9) code for rhabdomyolysis; (2) had a statin prescription within 3 months before an ICD-9 code for an ADR from a lipid-lowering drug or a creatine kinase level of 1000 U/L or higher (to convert to µkat/L, multiply by 0.0167) in the GHC laboratory database; and (3) were identified by natural language processing software as having the words “rhabdo” and “statin” appear near each other anywhere in the EMR. Statin-related rhabdomyolysis and myopathy were defined as muscle symptoms with a peak creatine kinase level 10 or more times and 5 to 10 times the upper limit of normal, respectively, in the absence of another etiology.

Incidence rates were calculated from the number of cases validated by EMR review divided by person-time of use for

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various doses of simvastatin and for all other statins combined. Among cases who switched statins, rhabdomyolysis was classified according to the statin being used at the time of symptom onset. Incidence rate ratios (IRR) comparing simvastatin with other statins and high with low doses of simvastatin were calculated by dividing the incidence rates for validated cases and rhabdomyolysis cases identified by ICD-9 code. Confidence intervals were estimated using Stata version 11.0 (StataCorp). This study was approved and a waiver of consent granted by the GHC institutional review board.

**Results.** Among 292 statin users with an ICD-9 code for rhabdomyolysis, 22 cases of statin-related rhabdomyolysis were validated (positive predictive value of 7.5% [95% CI, 5.0%-11.1%]; Table 1). Seven additional cases were identified by other methods for a sensitivity of 76% (95% CI, 58%-88%). Common etiologies for rhabdomyolysis other than statin use included prolonged immobility, arterial ischemia, recent surgery, and severe infection.

Of the 29 validated cases of statin-related rhabdomyolysis, 26 (90%) were hospitalized and 8 (29%) had at least a doubling of serum creatinine level; none died. The median peak creatine kinase level was 7450 U/L (interquartile range, 1477-150 510 U/L). Incidence rates are listed in Table 2. The rhabdomyolysis IRR for simvastatin compared with other statins was 2.61 (95% CI, 1.03-7.84) using validated cases compared with 1.03 (95% CI, 0.80-1.34) using the ICD-9 code for rhabdomyolysis. The IRR for dose of simvastatin of 80 mg/d or greater compared with 20 to 39 mg/d was 12.2 (95% CI, 3.6-52.3) using validated cases compared with 1.77 (95% CI, 1.05-2.88) using the ICD-9 code for rhabdomyolysis.

**Comment.** These results confirm in a community setting findings from a recent clinical trial that prompted the US Food and Drug Administration to issue a warning about the use of high-dose simvastatin. The ICD-9 code for rhabdomyolysis was nonspecific for this ADR, and the resulting misclassification markedly attenuated the estimated relative risk for high-dose vs low-dose simvastatin.

### Table 1. Statin-Related Rhabdomyolysis and Myopathy Cases Identified Using Administrative Data

<table>
<thead>
<tr>
<th>Case-Identification Method</th>
<th>No. of Potential Cases Reviewed</th>
<th>No. of Validated Cases Rhabdomyolysis (n = 29)</th>
<th>Myopathy (n = 18)</th>
<th>Positive Predictive Value, % (95% CI)</th>
<th>Rhabdomyolysis</th>
<th>Myopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhabdomyolysis ICD-9 code&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Inpatient 250</td>
<td>18</td>
<td>2</td>
<td>7.2 (4.6-11.1)</td>
<td>0.8 (0.2-2.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Outpatient 42</td>
<td>4</td>
<td>0</td>
<td>9.5 (3.822.1)</td>
<td>0 (0-8.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total 292</td>
<td>22</td>
<td>2</td>
<td>7.5 (5.0-11.1)</td>
<td>0.7 (0.2-2.5)</td>
<td></td>
</tr>
<tr>
<td>Other criteria</td>
<td>Adverse event of lipid agent ICD-9 code&lt;sup&gt;b&lt;/sup&gt;</td>
<td>30</td>
<td>1</td>
<td>0</td>
<td>3.3 (0.6-16.7)</td>
<td>0 (0-11.4)</td>
</tr>
<tr>
<td></td>
<td>Creatine kinase ≥1000 U/L</td>
<td>39</td>
<td>1</td>
<td>10</td>
<td>2.6 (0.5-13.2)</td>
<td>25.6 (14.6-41.1)</td>
</tr>
<tr>
<td></td>
<td>Natural language processing</td>
<td>438</td>
<td>5</td>
<td>6</td>
<td>1.1 (0.5-2.6)</td>
<td>1.4 (0.6-3.0)</td>
</tr>
<tr>
<td></td>
<td>Total 507</td>
<td>7</td>
<td>16</td>
<td>1.4 (0.7-2.8)</td>
<td>3.2 (2.0-5.1)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Defined as a creatine kinase level 10 or more times the upper limit of normal.<br><sup>b</sup>Defined as a creatine kinase level 5 to 10 times the upper limit of normal.<br><sup>c</sup>The International Classification of Diseases, Ninth Revision (ICD-9) code is 728.88.<br><sup>d</sup>The ICD-9 code is E942.2.

### Table 2. Incidence Rates for Statin-Related Rhabdomyolysis and Myopathy

<table>
<thead>
<tr>
<th>Dose of simvastatin, mg/d</th>
<th>Person-Years of Use</th>
<th>No. of Validated Cases Rhabdomyolysis (n = 29)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Myopathy (n = 18)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Incidence Rates per 100 000 Person-Years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>21 832</td>
<td>0</td>
<td>0</td>
<td>0 (0-16.9)</td>
</tr>
<tr>
<td>20-39</td>
<td>75 082</td>
<td>4</td>
<td>2</td>
<td>5.3 (1.5-13.6)</td>
</tr>
<tr>
<td>40-79</td>
<td>56 703</td>
<td>8</td>
<td>4</td>
<td>14.1 (6.1-27.8)</td>
</tr>
<tr>
<td>≥80</td>
<td>16 876</td>
<td>11</td>
<td>4</td>
<td>64.8 (32.3-116.0)</td>
</tr>
<tr>
<td>All doses</td>
<td>170 605</td>
<td>23</td>
<td>10</td>
<td>13.5 (8.6-20.2)</td>
</tr>
<tr>
<td>Other statins&lt;sup&gt;c&lt;/sup&gt;</td>
<td>116 154</td>
<td>6</td>
<td>8</td>
<td>5.2 (1.9-11.2)</td>
</tr>
<tr>
<td>All statins</td>
<td>286 758</td>
<td>29</td>
<td>18</td>
<td>10.1 (7.8-14.5)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Defined as a creatine kinase level 10 or more times the upper limit of normal.<br><sup>b</sup>Defined as a creatine kinase level 5 to 10 times the upper limit of normal.<br><sup>c</sup>Primarily lovastatin (69%) and atorvastatin (24%).
We did not adjust for potential confounding factors and may have failed to identify all cases of statin-related rhabdomyolysis, although these limitations are unlikely to account for the large relative risks. The use of administrative data alone in studies of ADRs with multiple causes may fail to detect actionable and clinically important harms.

James S. Floyd, MD, MS
Susan R. Heckbert, MD, PhD
Noel S. Weiss, MD, DrPH
David S. Carrell, PhD
Bruce M. Psaty, MD, PhD

Author Affiliations: Departments of Epidemiology (Drs Floyd, Heckbert, and Weiss) (jfloyd@uw.edu) and Medicine (Dr Psaty), University of Washington, Seattle, and Group Health Research Institute, Group Health Cooperative, Seattle, Washington (Dr Carrell).

Author Contributions: Dr Floyd had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Floyd, Heckbert, Psaty. Acquisition of data: Floyd, Heckbert, Carrell, Psaty. Analysis and interpretation of data: Floyd, Heckbert, Weiss, Psaty. Drafting of the manuscript: Floyd, Psaty. Critical revision of the manuscript for important intellectual content: Floyd, Heckbert, Weiss, Carrell, Psaty. Statistical analysis: Floyd.

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