A Population-Based Study of Simvastatin Drug-Drug Interactions in Cardiovascular Disease Patients

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Abstract

Simvastatin is a commonly used medication for lipid management and cardiovascular disease, however, the risk of adverse events (AEs) with its use increases via drug-drug interaction (DDI) exposures. Patients were extracted if initially diagnosed with cardiovascular disease and newly initiated simvastatin therapy. The cohort was divided into a DDI-exposed group and a non-DDI exposed group. The DDI-exposed group was further divided into gemfibrozil, clarithromycin, and erythromycin exposure groups. The outcome was defined as a composite of predefined AEs. Our results show that the simvastatin-DDI group had a higher illness burden with longer simvastatin exposure time and more medical care follow-up compared with the simvastatin-non-DDI exposed group. AEs occurred more frequently in subjects exposed to interacting drugs with a higher risk for clarithromycin and erythromycin exposed subjects than for gemfibrozil subjects.

1. Introduction

Statins are commonly used to lower cholesterol levels for cardiovascular disease (CVD) patients in the primary and secondary prevention of acute events1-3. The percentage of American adults over age 40 using statins increased from 18% to 26% during 2003-20124. Based on the American College of Cardiology and the American Heart Association guidelines, an estimated 26.4 million U.S. adults could benefit from statin use5. Although statins are generally well tolerated and show a relatively good safety profile, concerns have been raised regarding statin-associated adverse events (AEs) especially muscle related events6-7, leading to medication non-adherence and discontinuation8. More generally, drug-drug interactions (DDIs) are a common cause of AEs which are responsible for up to 2.8% of hospital admissions9. Drugs that can interrupt the absorption, distribution, metabolism, or excretion of statin medications may cause a statin-drug interaction. Many CVD patients may need statins as well as other therapies, especially in those who have multiple comorbidities, and those at high CVD risk who cannot achieve optimal therapeutic benefits from statin monotherapy10-12. The prevalence of exposure to all potential statin-drug interactions is above 20%13. Cytochrome P450 3A4 (CYP3A4) is the major enzyme responsible for the most statin medication metabolism14-16. The interactions between statins and CYP3A4 inhibitors are well established17-19. In addition to CYP3A4, the organic anion transporting polypeptide 1B1 (OATP1B1) has also been known to transport all statins from plasma into hepatocyte for metabolism and elimination20-26. Hence, drugs that potentially inhibit OATP transporters may also increase the plasma concentration of statins and thus may increase the risk of AEs.
In this study, we focused on simvastatin as it is one of the earliest statins that was approved by Food and Drug Administration (FDA) and has a long history of medical application. Data showed that simvastatin was one of the most commonly prescribed statins. According to our data, atorvastatin (40.4%) and simvastatin (36.1%) are the top two most prescribed statin agents. However, simvastatin undergoes more pre-systemic metabolism than atorvastatin, which results in lower bioavailability for simvastatin (<=5%) compared with atorvastatin (12%). Drugs with high intestinal and liver extraction are often involved in significant DDIs when concomitant use with enzyme inhibitors or inducers. Therefore, simvastatin is more susceptible to drug-drug interactions than atorvastatin. Study showed simvastatin blood levels may be increased five-fold or higher by CYP3A4 inhibitors. In addition, FDA restricted the use of the highest approved dose of simvastatin (80mg) because of its increased risk of muscle related events. FDA recommended that “simvastatin 80 mg should be used only in patients who have been taking this dose for 12 months or more without evidence of muscle injury (myopathy)”. Given the innate characteristics of simvastatin, its long history of use and large number of individuals using the medication, it is an important medication on which to assess the risk of AEs associated with DDI exposures.

The purpose of this retrospective study was to evaluate the effect of the combination therapy of simvastatin and several pre-defined high risk interacting drugs, which belong to CYP3A4 and/or OATP inhibitors, on CVD patients using simvastatin medications for secondary prevention in a large administrative claims dataset. Many case reports also investigated the AEs associated with statins DDIs. However, they either focused on composite statin use or composite interacting drugs which cannot be able to present the interactions between specific statin and interacting drug. Better evidence on actual DDI risk is needed to help in addressing problems of DDI risk alerting consistency which is important problem for both patients and providers. Our study extends these findings by focusing on one specific statin (simvastatin) and several predefined high risk interacting drugs. To better understand the interactions between simvastatin and specific interacting drugs, three drugs which were known metabolic inhibitors were selected for subgroup analysis due to their relatively large sample size with adequate power for statistical analysis. In addition, to the best of our knowledge, no published population-based study specifically differentiated among different time periods: pre-DDI, DDI exposure, and post-DDI time periods. Comparisons between the DDI-exposed group and non-DDI-exposed groups as well as the comparisons within subjects among those with DDI-exposure including pre-DDI, DDI exposure, and post-DDI time frames were performed.

2. Methods

2.1. Data source

We conducted a retrospective population-based cohort study using de-identified administrative claims data from the OptumLabs® Data Warehouse (OLDW), which includes medical and pharmacy claims, laboratory results, and enrollment records for commercial and Medicare Advantage (MA) enrollees. The database contains longitudinal health information on enrollees and patients, representing a diverse mixture of ages, ethnicities and geographical regions across the United States. Since this study involved analysis of pre-existing, de-identified data, it was exempt from Institutional Review Board approval.

2.2. Interacting drugs

The interacting drugs were selected by clinical expert review after carefully screening available DDI resources including drugs.com, Lexicomp, and Epocrates, and published literature. Drugs that had the highest DDI risk across each of the DDI resources were selected, including clarithromycin, telithromycin, erythromycin, nefazodone, itraconazole, ketoconazole, posaconazole, boceprevir, danazol, cobicistat, gemfibrozil, and cyclosporine. These medications are CYP3A4 and/or OATP inhibitors and had been previously identified as increasing risk of AEs with simvastatin.

To investigate the safety of specific interacting drugs, a subgroup analysis was conducted among three interacting drugs - gemfibrozil, clarithromycin, and erythromycin, as they had a relatively large number of patients with adequate power for statistical analysis.

2.3. Study population

Claims data adjudicated between January 2010 and September 2015 were investigated in the study. Cohort patients were extracted based on the following inclusion and exclusion criteria: 1) age >= 40 years old, 2) no CVD diagnosis and simvastatin prescriptions within one year prior to the CVD index date, 3) initiating simvastatin therapy within
30 days of the CVD index date, 4) continuous one year medical and pharmacy enrollment before the CVD index
date and 1 year and 1 month after statin index date, and 5) no simvastatin treatment transitions during the study
period. Statin transitions were present when a subject had either a change in statin medication or a change in statin
medication dosage. It was necessary to limit the study to subjects without transitions in order to develop the
personalized treatment model in the prior study on this cohort. This approach also helps to focus on the DDI effect
on the same statin treatment. The study period was from the simvastatin initiation date to the end of the treatment or
the completion of one year, whichever occurs first. Treatment end date was identified when the persistent nonuse
gap between two simvastatin prescriptions was longer than 30 days. We used a >30-day gap to determine non-
adherence based on the usage patterns in the cohort population, 85.9% of the claims had 30 days of supply and only
14.1% had 60-days or 90 days of supply. Other detailed information such as the rational of the above criteria on the
study cohort development can be found in our previous study and methods descriptions40,41.

The patient cohort was divided into two groups according to whether they were exposed to the predefined high risk
interacting drugs: DDI group (exposed to an interacting drug) and non-DDI group (not exposed to an interacting
drug). DDI group patients were identified when concomitant administration of at least one interacting drug during
the simvastatin exposure period. The concomitant medication is defined as occurring when the prescriptions of
simvastatin and interacting drug had an overlapping exposure period. Patients who took two or more different
interacting drugs during simvastatin exposure were excluded because they had a complex pre-DDI and post-DDI
period and a very small sample size (N<11). Results based on very small numbers are often meaningless. In addition,
to protect patient privacy and confidentiality, small numbers or small percentages which represent small numbers
(N<11) cannot be reported according to the OptumLabs cell size suppression policy.

2.4. Study time frames definition
For patients in the DDI group, the study period was divided into three time frames: 1) pre-DDI which was prior to
initiation of DDI agent, 2) DDI exposed period which was while the patient took simvastatin and an interacting
medication, and 3) post-DDI which was after the DDI exposure ended.

2.5. Outcome measurement
The International Classification of Diseases–9th Revision, Clinical Modification (ICD-9-CM) was used to identify
AEs. Major clinically important AEs, including rhabdomyolysis, myopathies, renal AEs, hepatic AEs, and
medication poisoning events associated with statin medication use were considered. The ICD-9-CM codes that we
used to identify these events can be found in our previous study40.

Incidence rates (IRs), which accounts for the potential difference of length of drug exposure, were used to evaluate
the risk of AEs in different groups. IRs were reported as the number of cases per 10 person-years of exposure.
Incidence rate ratio (IRR) was used to compare IRs between groups. We used it to evaluate if DDI group had a
higher IR than non-DDI group, and assess if clarithromycin or erythromycin (CYP3A4 and OATP inhibitors) had a
higher IRs than gemfibrozil (OATP inhibitor) as double drug pathway may have a greater effect on simvastatin than
single drug pathway.

The number of physician claims per month was used as another study outcome to assess if patients with DDI
exposure had increased clinical follow-up to manage the potential DDI risk compared with non-DDI group since
they were exposed to well known interacting medications and it was hypothesized that subjects exposed to the
interactions would have more intense medical follow-up. Physician claims on the same day are counted as one claim.
Outpatient claims, emergency room (ER) visits, and office visits were included in the physician claim totals.

2.6. Statistical analysis
R software was used for analysis. Two-tailed t-students tests were performed for continuous variables. 95%
confidence intervals (CI) were calculated for IRR. Analyses were carried out with RStudio version 0.98.1103. A p-
value < 0.05 was considered statistically significant.

3. Results
13,801 new simvastatin CVD patients, who did not have any interacting drug or had only one interacting drug
exposure, were included in this study. A total of 264 patients were identified in the DDI group including 112
clarithromycin patients, 106 gemfibrozil patients, 32 erythromycin patients, and a total of 14 patients who took
ketoconazole, nefazodone, cyclosporine, or itraconazole. No patient used telithromycin, posaconazole, boceprevir,
danazol, or cobicistat.
3.1 Baseline comparison between DDI group and non-DDI group

A comparison of baseline patient characteristics between simvastatin DDI group and non-DDI group is shown in Table 1. From the table, we can see the DDI group has a significantly longer statin exposure time and higher Charlson score than the non-DDI group. The IRR for DDI group to non-DDI group is 1.29 (IRR=1.29, 95% CI: 0.78-2.14). Table 2 shows IRs comparison between DDI and non-DDI group. DDI group had a 1.29 times higher incidence risk of AEs compared with the non-DDI group after adjusting for statin exposure time.

3.2 Physician claims comparisons

Table 3 shows the results of the numbers of physician claims per month. Patients who did not have any physician claims were counted as contributing zero visits. Among the patient cohort, 642 patients (4.7%) resulted zero visits. Since only a small percentage of the cohort had zero visits, they were included in the following analysis. Our results show that the DDI group has a significantly higher number of physician claims than the non-DDI group (2.53 claims/month vs. 2.17 claims/month with p=0.0060). Similar analysis had been done among the DDI group patients. 38 of 264 patients concomitantly use an interacting drug throughout the whole simvastatin period resulting in zero days of DDI unexposed time period. The number of physician claims per month during the DDI exposed and unexposed time period are 3.95 and 2.38, respectively, with a statistically significant p-value less than 0.0001. A significant result was also found when comparing the two DDI unexposed time periods - a higher number of physician claims in the pre-DDI period (3.22 claims per month) compared with the post-DDI period (1.91 claims per month).

Table 1. Comparison of the patient baseline characteristics between DDI group and non-DDI group.

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>DDI Group (N=264)</th>
<th>Non-DDI Group (N=13,537)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin exposure time (days)</td>
<td>249.1</td>
<td>204.0</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63.9</td>
<td>64.9</td>
<td>0.1555</td>
</tr>
<tr>
<td>Male (%)</td>
<td>162 (61.4%)</td>
<td>7,934 (58.6%)</td>
<td>0.3646</td>
</tr>
<tr>
<td>Charlson index score</td>
<td>1.55</td>
<td>1.10</td>
<td>0.0002*</td>
</tr>
<tr>
<td>Intensity (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>30 (11.4%)</td>
<td>1,719 (12.7%)</td>
<td>0.5003</td>
</tr>
<tr>
<td>Medium</td>
<td>220 (83.3%)</td>
<td>11,226 (82.9%)</td>
<td>0.8616</td>
</tr>
<tr>
<td>High</td>
<td>14 (5.3%)</td>
<td>592 (4.4%)</td>
<td>0.505</td>
</tr>
</tbody>
</table>

* Results are significantly different.

Table 2. Incidence rate ratio comparison between DDI and Non-DDI groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>AE Counts e</th>
<th>IRa</th>
<th>IRRb [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-DDI group (N=13,537)</td>
<td>1,957</td>
<td>2.84</td>
<td></td>
</tr>
<tr>
<td>DDI group (N=264)</td>
<td>13</td>
<td>3.66</td>
<td>1.29 [0.75, 2.22]</td>
</tr>
</tbody>
</table>

Note:  
a. IR = incidence rate  
b. IRR = incidence rate ratio  
c. In DDI group, AEs were counted when they occurred during DDI exposure period. In Non-DDI group, AEs were counted when they occurred during the whole study period.

Table 3. Physician claims comparisons.

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Group</th>
<th>Claim Number per Month (N)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>DDI group</td>
<td>2.53 (N=264)</td>
<td>0.0060*</td>
</tr>
<tr>
<td></td>
<td>Non-DDI group</td>
<td>2.17 (N=13,537)</td>
<td></td>
</tr>
<tr>
<td>DDI patients</td>
<td>DDI exposed period</td>
<td>3.95 (N=264)</td>
<td>&lt;0.0001*</td>
</tr>
</tbody>
</table>
** DD unexposed period includes both pre-DDI and post DDI periods.

### Baseline comorbidities comparisons

The above IRR and physician claim comparisons did not adjust for comorbidities, thus we compared individual Charlson comorbidity between DDI and non-DDI group to get a better sense whether the differences may be able to explained by underlying comorbidities or are more likely to be explained by DDI. Table 4 shows DDI group has significantly higher percentage of patients with chronic pulmonary disease, rheumatologic disease, and diabetes (mild to moderate). However, liver and renal disease, which could potentially affect the AEs during medication exposure, does not show statistically significance.

#### Table 4. Baseline comorbidities comparison between DDI and Non-DDI groups.

<table>
<thead>
<tr>
<th>Charlson Comorbidities</th>
<th>DDI Group, % (N=264)</th>
<th>Non-DDI Group, % (N=13,537)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>&lt;4.2%</td>
<td>3.7%</td>
<td>NS1</td>
</tr>
<tr>
<td>Renal disease</td>
<td>4.9%</td>
<td>4.9%</td>
<td>0.9974</td>
</tr>
<tr>
<td>Moderate or severe liver disease</td>
<td>&lt;4.2%</td>
<td>0.14%</td>
<td>NS1</td>
</tr>
<tr>
<td>Mild liver disease</td>
<td>4.9%</td>
<td>3.1%</td>
<td>0.1657</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>5.7%</td>
<td>6.4%</td>
<td>0.6240</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>11.7%</td>
<td>8.1%</td>
<td>0.0687</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>8.3%</td>
<td>7.8%</td>
<td>0.7441</td>
</tr>
<tr>
<td>Dementia</td>
<td>&lt;4.2%</td>
<td>0.92%</td>
<td>NS1</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>23.5%</td>
<td>16.1%</td>
<td>0.0052*</td>
</tr>
<tr>
<td>Rheumatologic disease</td>
<td>9.1%</td>
<td>2.8%</td>
<td>0.0005*</td>
</tr>
<tr>
<td>Peptic ulcer disease</td>
<td>&lt;4.2%</td>
<td>0.85%</td>
<td>NS1</td>
</tr>
<tr>
<td>Diabetes (mild to moderate)</td>
<td>31.4%</td>
<td>18.9%</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Diabetes with chronic complications</td>
<td>6.8%</td>
<td>4.4%</td>
<td>0.1296</td>
</tr>
<tr>
<td>Paraplegia or hemiplegia</td>
<td>&lt;4.2%</td>
<td>0.48%</td>
<td>NS1</td>
</tr>
<tr>
<td>Any malignancy, including lymphoma and leukemia</td>
<td>9.1%</td>
<td>7.8%</td>
<td>0.4839</td>
</tr>
<tr>
<td>Metastatic solid tumor</td>
<td>&lt;4.2%</td>
<td>0.73%</td>
<td>NS1</td>
</tr>
<tr>
<td>AIDS</td>
<td>&lt;4.2%</td>
<td>0.15%</td>
<td>NS1</td>
</tr>
</tbody>
</table>

Note: 1: NS: not significant. Small numbers or small percentages which represent small numbers (N<11) cannot be reported according to the OptumLabs cell size suppression policy. The corresponding p-values are replaced by NS if p-value is >0.05.

### Relationship between DDI exposure time and adverse event rates

The estimated percentages of patients who had any type of AEs during DDI exposure period are shown in Figure 1. A temporal association of percentage of AE patients with DDI exposure time was assessed. DDI group patients were divided into six groups based on the length of DDI exposure time (1-7 days, 8-15 days, 16-30 days, 31-90 days, 91-270 days, and 271-365 days) to provide a general time frame for the occurrence of AEs. This figure indicates the number of people who have AE increases as the DDI exposure time increases.
Figure 1. Estimated percentage of AE patients with DDI exposure time.

3.4 Subgroup analysis in three specific interacting drugs

Table 5 shows the results of the three specific interacting drugs in DDI group: gemfibrozil, clarithromycin, and erythromycin. IRs were measured in pre-DDI, DDI exposure, and post-DDI time periods. Person time was calculated as the total time from the start date to the date of index AE occurred or to the end of each time period, whichever occurs first. IRRs were calculated using IR of non-DDI group (2.84 per 10 person-year) as the reference group.

Both clarithromycin and erythromycin have higher IRs in all three time frames compared with non-DDI group. Gemfibrozil DDI group has significantly higher IR in the pre-DDI and DDI exposure period, but lower IRs in the post-DDI period (not significant) compared with the non-DDI group. The risks of AEs for clarithromycin and erythromycin were higher than gemfibrozil during DDI exposure and post-DDI time. However, gemfibrozil had the highest pre-DDI IR compared with the other two interacting drugs. The highest IRs of clarithromycin and erythromycin occurred in the DDI exposed period. However, the highest IR of gemfibrozil occurred in the pre-DDI time period.

Table 5. Risk estimate in concomitant use of simvastatin and interacting drugs.

<table>
<thead>
<tr>
<th>Interacting Drugs (N)</th>
<th>Time Frames</th>
<th>IRs</th>
<th>IRRs** [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemfibrozil (N=106)</td>
<td>Pre DDI</td>
<td>8.84</td>
<td>3.11 [1.17, 8.30]*</td>
</tr>
<tr>
<td></td>
<td>DDI exposure</td>
<td>3.11</td>
<td>1.10 [0.57, 2.11]</td>
</tr>
<tr>
<td></td>
<td>Post DDI</td>
<td>1.51</td>
<td>0.53 [0.23, 1.63]</td>
</tr>
<tr>
<td>Clarithromycin (N=112)</td>
<td>Pre DDI</td>
<td>3.26</td>
<td>1.15 [0.65, 2.02]</td>
</tr>
<tr>
<td></td>
<td>DDI exposure</td>
<td>6.09</td>
<td>2.14 [0.54, 8.58]</td>
</tr>
<tr>
<td></td>
<td>Post DDI</td>
<td>3.64</td>
<td>1.28 [0.74, 2.21]</td>
</tr>
<tr>
<td>Erythromycin (N=32)</td>
<td>Pre DDI</td>
<td>4.69</td>
<td>1.65 [0.69, 3.97]</td>
</tr>
<tr>
<td></td>
<td>DDI exposure</td>
<td>16.04</td>
<td>5.65 [1.41, 22.60]*</td>
</tr>
<tr>
<td></td>
<td>Post DDI</td>
<td>3.48</td>
<td>1.23 [0.46, 3.27]</td>
</tr>
</tbody>
</table>

Note: * Results are significantly different.

** IRRs were calculated to compare with the IR of non-DDI group which is 2.84 per 10 person-year.

4. Discussion
The drug interactions between statins and CYP3A4 and/or OATP1B1 inhibitors are well recognized. However, studies that focus on the interactions between simvastatin and specific interacting drugs are very limited. We pre-selected several high-risk of CYP3A4 and/or OATP1B1 inhibitors and conducted a population-based study using administrative claims data to explore the actual exposures and risks of AEs in CVD patients who were prescribed simvastatin combination therapy with these pre-specified high risk interacting drugs. Given the well-described risk associated with these DDI exposures, it was expected that there would be very few individuals using these medication combinations. It was also expected that if these combinations were prescribed that there would be a need for greater clinical follow-up to monitor for potential adverse drug events related to DDI exposure. We also did a subgroup analysis to investigate the interactions between simvastatin and three specific interacting drugs that few previous studies had evaluated and had substantial numbers of DDI-exposures in the study cohort. Our study used the real world data to provide empirical data on the actual risk of DDI exposure, the length of exposure, and the risk of clinically significant AEs.

The baseline Charlson index score and simvastatin exposure time in the DDI group were significantly higher than the non-DDI group indicating the DDI group was a sicker population with longer simvastatin exposure time. DDI group had more medical follow-up than non-DDI group with a statistically significant result. The AE incidence rate in the DDI group is higher than the non-DDI group but was not statistical significant. Although results are not adjusted for Charlson comorbidity score, we compared the individual comorbidity between DDI and non-DDI group. We found baseline liver and renal disease, which could potentially affect the AEs during medication exposure, are not statistically different. This may indicate the differences between the two groups are more likely to be explained by DDI, however, the increased comorbidities among those with DDI exposures may also contribute to a greater risk of illness include adverse drug events.

Within the DDI group, the number of physician claims during the DDI exposed time period was more than that during the DDI unexposed time period. This indicates patients were receiving more medical care during the concomitant administration of simvastatin and interacting medications, potentially providing important clinical monitoring or physician visits for AEs. When comparing the pre-DDI and post-DDI time periods, the results showed patients generally had more physician claims in pre-DDI than post-DDI time period. This may be due to patients having more intense physician follow-up in the months after the index CVD event to provide needed medication adjustments and control of cardiovascular risk factors. This study also showed that the number of patients with AEs increased with DDI exposure time which indicates longer DDI exposure may induce higher risk of AEs.

When comparing the three inhibitors, we found clarithromycin and erythromycin had higher risk of AEs than gemfibrozil during DDI therapy. This may be because both clarithromycin and erythromycin are potent inhibitors of CYP3A4 and OATP1B1, leading to a greater total effect on simvastatin by influencing two clinically important drug pathways. Gemfibrozil, on the other hand, is primarily dependent on OATP inhibition but not CYP3A4 leading to a weaker overall inhibition. An interesting finding about gemfibrozil was it had the highest AE IR during pre-DDI time period compared with the other two inhibitors. Patients in gemfibrozil group may have a different pattern of hyperlipidemia (high Triglycerides, low HDL and high LDL) than patients that don’t receive gemfibrozil. In addition, we explored the basic characteristics among the three groups. We found that the gemfibrozil group had substantially higher percentage of male patients (72.6%) compared with clarithromycin (55.4%) and erythromycin (46.9%), which indicates the differences may be due to gender differences reflecting potentially different hormonal influences and associated pharmacogenomics. Likewise, the dropout rate in gemfibrozil patients is the highest (17%) among all the three groups.

Our findings are consistent with one population-based cohort study which was conducted in Canada showing that the co-prescription of a statin metabolized by CYP3A4 with clarithromycin or erythromycin was associated a higher risk of hospitalization with rhabdomyolysis, acute kidney injury, or all-cause mortality compared with azithromycin. Their outcomes were based on a composite of atorvastatin, simvastatin, and lovastatin and a composite of clarithromycin and erythromycin. Our study focused on one specific statin (simvastatin) and analyzed the three inhibitors individually to extend on these previous findings. Kellick et al. pointed out that gemfibrozil had a less profound effect on the statin medications that involve complete inhibition of CYP3A4 and OATP1B1 because it only inhibits OATP1B1. In contrast, Meggarpour et al. found the risk for hospitalization or death in persons receiving clarithromycin is not causally associated with the interactions between statins (atorvastatin, simvastatin, or lovastatin) and clarithromycin. Another cohort study focused on the concomitant use of statins and fibrates indicating that the combination therapy of simvastatin and gemfibrozil increased the incidence of rhabdomyolysis hospitalizations.
Our study used the OptumLabs Data Warehouse that included both commercial and Medicare Advantage enrollees for analysis. This database provides the ability to detect rare drug-related AEs such as rhabdomyolysis. Although it has important advantages, there are several limitations: 1) diagnostic coding limitations such as disease severity cannot reliably inferred from the diagnosis codes; 2) claims data documents clinical events via diagnosis codes and procedure codes which may not capture all the events since some events may not have reimbursement like a patient calling their provider or patients who did not seek medical attention or stopped therapy. Thus, we likely underestimated the total risk; 3) drug information was extracted from filled pharmacy claims, but we cannot guarantee patients actually took the prescribed drugs; 4) Patients may be misclassified when a) AEs were not simvastatin-related AEs or caused by other interacting factors such as food (grapefruit juice) and underlying clinical diseases (liver disease and renal dysfunction); b) the initial AEs happened before starting interacting drugs and the follow-up visits that occurred after initiating interacting drugs were identified as AEs due to timing accuracy problems; c) events were not captured by the medical codes; 5) results that are based on the small size group, e.g. erythromycin, are difficult to draw meaningful conclusions; 6) the associations based on observational study may not be causal. Finally, since the study population only included subjects with a stable statin dosage, there may be selection bias, however, it is not clear if this is likely to affect the occurrence of AEs in either the DDI or non-DDI exposed groups, but may affect generalizability of the findings.

5. Conclusions

The potential statin-drug interactions in CVD patients are common and should be monitored to limit patient AEs. The risk of AEs is amplified when concomitant administration occurs with simvastatin and clarithromycin or erythromycin, which is likely due to the multiple paths to create drug interactions. The combination of simvastatin and gemfibrozil yield fewer AEs than the combination with clarithromycin or erythromycin which may be due to single pathway inhibition. If possible, these inhibitors, especially clarithromycin and erythromycin, should be avoided in clinical settings when patients take simvastatin due to the risk of AEs.

References

8. Ellis JJ, Erickson SR, Stevenson JG, Bernstein SJ, Stiles RA, Fendrick AM. Suboptimal statin adherence and discontinuation in primary and secondary prevention populations: Should we target patients with the most to gain? J Gen Intern Med [Internet]. 2004;
12. Bottorff MB. Statin safety and drug interactions: clinical implications. Am J Cardiol [Internet]. 2006;
14. Prueksaritanont T, Ma B, Yu N. The human hepatic metabolism of simvastatin hydroxy acid is mediated...
primarily by CYP3A, and not CYP2D6. Br J Clin Pharmacol [Internet]. 2003;
22. Choi HY, Bae KS, Cho SH, et al. Impact of CYP2D6, CYP3A5, CYP2C19, CYP2A6, SLCO1B1, ABCB1, and ABCG2 gene polymorphisms on the pharmacokinetics of simvastatin and simvastatin acid. Pharmacogenet Genomics [Internet]. 2015;
27. FDA. Guidance for industry. Drug interaction studies study design, data analysis, implications for dosing, and labeling recommendations. Guid Doc [Internet]. 2012;
28. FDA. FDA Drug Safety Communication: New restrictions, contraindications, and dose limitations for Zocor (simvastatin) to reduce the risk of muscle. US Food Drug Adm [Internet]. 2013;
32. Molden E, Andersson KS. Simvastatin-associated rhabdomyolysis after coadministration of macrolide antibiotics in two patients. Pharmacotherapy [Internet]. 2007;
38. OptumLabs. OptumLabs and OptumLabs Data Warehouse (OLDW) Descriptions and Citation. Cambridge, MA n.p [Internet]. 2018;PDF. Reproduced with permission from OptumLabs.
42. Lynch T, Price A. The effect of cytochrome P450 metabolism on drug response, interactions, and adverse effects. Am Fam Physician [Internet]. 2007;
43. Rodrigues a D, Roberts EM, Mulford DJ, Yao Y, Ouellet D. Oxidative Metabolism of Clarithromycin in the Presence of Human Liver Microsomes. Drug Metab Dispos [Internet]. 1997;
44. Seithel A, Eberl S, Singer K, et al. The influence of macrolide antibiotics on the uptake of organic anions and drugs mediated by OATP1B1 and OATP1B3. Drug Metab Dispos [Internet]. 2007;