RESEARCH

Results of a Safety Initiative for Patients on Concomitant Amiodarone and Simvastatin Therapy in a Veterans Affairs Medical Center

Sahar Karimi, PharmD; Augustus Hough, PharmD; Cherylyn Beckey, PharmD, BCPS, CDE; and David Parra, PharmD, FCCP, BCPS

ABSTRACT

BACKGROUND: The FDA revised the labels of amiodarone and simvastatin in 2002 to warn of increased risk of rhabdomyolysis, the most severe form of myopathy, when the 2 drugs are taken concomitantly in doses greater than 20 milligrams (mg) per day of simvastatin. The FDA reissued the warning in 2008 after receiving reports of 52 cases of rhabdomyolysis in the Adverse Event Reporting System (AERS) after the label changes in 2002 and suggested use of an alternative statin for patients receiving amiodarone who require more than 20 mg simvastatin to attain lipid goals.

OBJECTIVES: To (a) assess the prevalence of concomitant amiodarone and simvastatin in doses greater than 20 mg per day and the frequency of additional risk factors for myopathy in these patients, and (b) implement and evaluate a protocol to convert patients receiving this combination to alternative statins.

METHODS: A review was conducted of all patients with active prescriptions for both simvastatin at doses greater than 20 mg per day and amiodarone from a Veterans Affairs (VA) medical center as of November 1, 2008. Data collected included demographics, duration of therapy, baseline lipid and aminotransferase values, and risk factors for myopathy (i.e., aged 80 years or older; female sex; small body frame; hypothyroidism; hepatic or renal insufficiency; diabetes; alcohol abuse; and use of medications, such as gemfibrozil and nicotinic acid, that may increase the risk of myopathy). Patients were converted to either pravastatin or rosuvastatin based on baseline simvastatin dose, low-density lipoprotein cholesterol (LDL-C) level, and renal function. The conversion protocol was developed to maintain LDL-C lowering with potentially safer statins. Follow-up lipid and aminotransferase values were collected as customary clinical markers of efficacy and safety, respectively, for patients converted per the protocol. Because creatine kinase values are not routinely assessed in clinical practice, they were not available as part of the current protocol.

RESULTS: Of the 48,612 patients who accessed the pharmacy in this VA medical center, 17,760 (36.5%) had an active order for simvastatin 40 mg or 80 mg per day, and 92 of these patients (0.52%) also had an active order for amiodarone. These patients were prescribed simvastatin primarily for secondary prevention (88 [95.7%] with coronary artery disease [CAD] as the indication for statin therapy), and were highly controlled with mean (SD) baseline LDL-C of 71 (21) mg per deciliter. The mean (median) duration of therapy on the combination of amiodarone plus simvastatin 40 mg or more per day was 43 (37) months. Of the 92 patients, 26 (28.3%), 35 (38.0%), and 18 (19.6%) patients had 1, 2, or 3 or more additional risk factors for myopathy, respectively. 16 patients were not converted per protocol to an alternate statin (4 were taken off amiodarone, 2 were taken off statin therapy, 6 had the simvastatin dose reduced to 20 mg per day or less, and 4 were converted to an alternate statin off-protocol), and 14 patients did not have follow-up laboratory values. For the 62 patients converted per protocol and with follow-up laboratory values, there were no statistically significant changes in mean lipid or aminotransferase values after conversion. One patient reported symptoms of myalgia after conversion to rosuvastatin; however, the conversion protocol did not require obtaining creatine kinase values.

CONCLUSION: 0.19% of patients (n=92) with pharmacy dispensing records in this VA facility in 2008 received amiodarone in combination with simvastatin in doses greater than 20 mg per day, and the majority of patients had additional risk factors for myopathy. There were no significant changes in mean laboratory values for lipids or aminotransferase for the 62 patients (67%) who were converted and who had baseline and follow-up values; there was 1 case of self-reported myalgia in a patient converted to rosuvastatin.

J Manag Care Pharm. 2010;16(7):472-81

What is already known about this subject

- Myopathy occurs in 1.5%-5% of patients in randomized controlled clinical trials with statins. However, observational studies suggest that mylagia may occur in as many as 10% of statin users, but rhabdomyolysis, the life-threatening form of myopathy, is rare.
- In 2002, the FDA added a warning to the label of simvastatin (Zocor) that recommended it not be used in doses exceeding 20 mg per day in combination with amiodarone (Pacerone).
- In August 2008, the FDA reissued a safety alert regarding the increased risk for myopathy and rhabdomyolysis in patients receiving concomitant amiodarone and simvastatin in doses greater than 20 mg per day, citing 52 cases of rhabdomyolysis reported to the FDA in the Adverse Event Reporting System (AERS) for this drug combination that occurred after warnings to the labels of amiodarone and simvastatin were added in 2002: 26 (50%) were taking simvastatin 80 mg per day, 13 (25%) were taking simvastatin 40 mg per day, 4 (8%) were taking simvastatin 20 mg per day, and 1 patient was taking simvastatin 5 mg per day; 8 patients (15%) were taking an unknown dose of simvastatin.
- In the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH), 12,064 patients with a previous heart attack were randomized to simvastatin 80 mg per day (n=6,031) or simvastatin 20 mg per day (n=6,033), and the relative risk of definite myopathy or incipient myopathy (defined as "a creatine kinase level that was more than both 3 times the upper limit of the normal range and 5 times the baseline level, plus an alanine aminotransferase level that was more than 1.7 times the baseline value without an elevated alanine aminotransferase level alone at any other visit, irrespective of whether there were muscle symptoms") was 8.8 (95% CI=4.2-18.4) for concomitant simvastatin 80 mg and amiodarone versus simvastatin 80 mg alone.
- Observational and pharmacokinetic data suggest that pravastatin may be the safest initial therapeutic alternative to simvastatin in combination with amiodarone. The lack of significant interaction reports with rosuvastatin and amiodarone suggest its potential role as safer than simvastatin in patients who require a high-potency statin in combination with amiodarone.

What this study adds

- This is the first report to our knowledge of an intervention developed to reduce the risks associated with high-dose simvastatin (greater than 20 mg per day) in combination with amiodarone. Among patients taking high-dose simvastatin in combination with amiodarone, the proportion of patients with at least 1 additional risk factor for myopathy was high (85.9%).
- Although this study did not assess actual patient harm, there appears to be a continuing need to identify patients in health plans who are at risk of potential harm from combination therapy of amiodarone with simvastatin doses greater than 20 mg per day.

Statins are potent 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors that decrease low-density lipoprotein cholesterol (LDL-C) levels and have demonstrated morbidity and mortality benefit in secondary prevention of cardiovascular outcomes.[1-8] Although statins are generally well-tolerated, the adverse effects of myopathy and rhabdomyolysis can occur.[1] A challenge in reviewing muscle-related adverse events with statins includes a lack of consensus for the definitions of myopathy, myalgia, myositis, and rhabdomyolysis. Organizations such as the National Lipid Association (NLA) and U.S. Food and Drug Administration (FDA) provide definitions for myopathy that include a cut-off for creatine kinase (CK) elevation (i.e., 10 times the upper limit of normal), but the FDA definition does not include specific symptoms such as muscle pain or soreness that the NLA uses in conjunction with elevation of creatine kinase.[9] The most complete definition of muscle-related adverse events is found in the joint statement from the American College of Cardiology (ACC), American Heart Association (AHA), and National Heart, Lung, and Blood Institute (NHLBI), which defines myopathy broadly as "any disease of the muscles."[1] Myalgia and myositis are both characterized by muscle aches or weakness, with myositis also being defined by increased creatine kinase levels. Rhabdomyolysis is defined by the ACC/AHA/NHLBI joint statement as "muscle symptoms with marked elevation of creatine kinase," generally greater than 10 times the upper limit of normal, and with "creatinine elevation (usually with brown urine and urinary myoglobin)."[1] The FDA defines rhabdomyolysis as the presence of organ damage and creatine kinase greater than 50 times the upper limit of normal.[9]

The rates at which myopathy, myalgia, and rhabdomyolysis occur vary in the literature. In randomized controlled trials (RCTs), statin-associated myopathy can occur at an incidence of 1.5%-5%.[9] A large meta-analysis that included 21 double-blind RCTs and 48,138 patients found no significant differences in the incidence of myalgia between subjects who received statins versus placebo.[10] Similar risk was seen in a review of 30 RCTs (n = 83,858), which showed similar rates for statins versus placebo for myositis (0.12% vs. 0.11%, respectively) and rhabdomyolysis (0.016% vs. 0.012%, respectively).[11] Rates of statin-associated myalgia range from 5% to 10% in observational studies.[9] Outpatient clinical practice data show that "muscle pain" symptoms are reported by up to 10% of outpatients receiving statin therapy.[12] This inconsistency makes it difficult to compare the reported rates of statin myopathy with actual clinical practice and may be due partly to the exclusion of patients with risk factors for myopathy in patient selection for statin RCTs.[9] Data from the FDA Adverse Event Reporting System (AERS) reveals an increase in myopathy reporting, from 0.38 cases per 1 million prescriptions in 1998 (0.43 in 1999 and 1.07 in 2000), rising to 3.56 cases per million in 2004 (0.74 in 2002 and 0.57 in 2003), possibly related to increased awareness following the U.S. market withdrawal of cerivastatin in 2001.[9,13] Therefore, muscle pain is not uncommon with statin therapy, myalgia may occur in 5%-10% of patients, and rhabdomyolysis although rare is clinically important because of the widespread use of statins and the possibility of renal failure and death when rhabdomyolysis is left untreated.[14]

While the exact mechanism of statin-induced myopathy is not well understood, it is known that risk increases with higher statin doses, use of medications that can increase serum statin levels, and the presence of other risk factors for myopathy (Table 1).[1,11,14] In 2002, the FDA revised the product labels of both amiodarone and simvastatin to warn of an increased risk of rhabdomyolysis when these drugs are used concomitantly.[15] However, even after the labeling change, the FDA continued to receive reports of rhabdomyolysis in patients on this combination and in 2008 reissued a warning about concomitant use of amiodarone and simvastatin in doses greater than 20 milligrams (mg) per day.[15]

Further insight into this interaction comes from the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH), in which interim analysis showed a strong association of myopathy in patients on concomitant amiodarone and simvastatin 80 mg per day (relative risk [RR] = 8.8, 95% confidence interval [CI] = 4.2-18.4).[16] This finding led to a protocol amendment in the SEARCH study in which patients on concomitant amiodarone and simvastatin 80 mg per day were decreased to simvastatin 20 mg per day.[17] The RR of myopathy with amiodarone and simvastatin 20 mg per day versus simvastatin 80 mg per day alone was lower for the remaining 5 years of the SEARCH study (RR = 3.5, 95% CI = 1.1-11.6).[16] These improved safety data following the SEARCH protocol amendment support the FDA's current recommendation to limit simvastatin doses to 20 mg daily when used concomitantly with amiodarone.

Several factors may contribute to the interaction between amiodarone and simvastatin, but the problem is likely associated with higher serum simvastatin levels. One postulated mechanism is the involvement of the cytochrome P450 (CYP) isoenzyme system.[18] Amiodarone is, among others, a

TABLE 1 Patient Characteristics and Risk Factors for Myopathy

Patient Characteristics (n = 92)	%	(n)
Mean [SD] age in years	78	[8]
Female sex	1.1	(1)
Compelling indication(s) for statin therapy[a]		
Coronary artery disease	95.7	(88)
Peripheral vascular disease	19.6	(18)
Diabetes	35.9	(33)
Cerebrovascular disease	27.2	(25)
Risk Factors for myopathy[a,b,c]	**Risk Factor Prevalence %**	**(n)**
Aged 80 years or older	43.5	(40)
Female sex in patients aged 80 years or older[d]	0	(0)
Small body frame (BMI < 18.5)[29]	0	(0)
Hepatic insufficiency[11]	0	(0)
Hypothyroidism[14]	31.5	(29)
Renal insufficiency (CrCl < 30 mL per min)[e]	12.0	(11)
Diabetes (documented diagnosis or use of antidiabetic medication)[11]	35.9	(33)
Active treatment for alcohol abuse	0	(0)
Positive AUDIT-C score[32]	17.4	(16)
Positive CAGE score (2 +)[33]	0	(0)
Medications that may increase myopathy risk		
Gemfibrozil	3.3	(3)
Nicotinic acid	19.6	(18)
Macrolides	4.3	(4)
Diltiazem[11]	3.3	(3)
Verapamil	0	(0)
Fenofibrate	0	(0)
Cyclosporine	0	(0)
Azoles[f]	0	(0)
Protease inhibitors[g]	0	(0)
Nefazodone	0	(0)
Risk factors for myopathy		
0	14.1	(13)
1	28.3	(26)
2	38.0	(35)
3 or more	19.6	(18)

[a]*Indications for statin therapy and presence of risk factors were not exclusive (all findings were recorded).*

[b]*The ACC/AHA/NHLBI joint clinical advisory statement was the primary source for the risk factors for myopathy;[1] and the sources for the other risk factors are cited individually.[11,14,29,32,33] These risk factors were assessed during the time period beginning on the date that the patient initially received amiodarone and simvastatin at a dose greater than 20 mg per day and ending on November 1, 2008.*

[c]*Prevalence documented as any diagnosis, positive score, or use during the duration of concomitant use of amiodarone and simvastatin doses greater than 20 mg per day.*

[d]*Advanced age, especially greater than 80 years old, in patients (females more than males) is a risk factor for myopathy. Therefore, female sex was included in the context of age greater than 80 years old as a risk factor for myopathy.[1]*

[e]*Renal function determined by Cockcroft-Gault formula with age, weight, and serum creatinine values defined by the values recorded nearest to the date of the search of pharmacy records for concomitant therapy.[30]*

[f]*Itraconazole, ketoconazole.*

[g]*Amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, ritonavir, saquinavir, tipranavir.*

ACC/AHA/NHLBI = American College of Cardiology/American Heart Association/National Heart, Lung, and Blood Institute; AUDIT-C = Alcohol Use Disorders Identification Test; BMI = body mass index; CAGE = cut-annoyed-guilty-eye (brief description of 4 scale items); CrCl = creatinine clearance; mL = milliliter.

CYP3A4 and CYP2C9 isoenzyme inhibitor and can increase serum simvastatin levels through decreased CYP3A4 metabolism, predisposing to myopathy and potentially rhabdomyolysis.[19] Concomitant use of amiodarone and any statin that undergoes extensive CYP3A4 or CYP2C9 metabolism could potentially increase the serum levels of that particular statin. Among the currently available statins, pravastatin (no CYP-mediated metabolism) and rosuvastatin (minor CYP2C9 metabolism, approximately 10%) are not extensively metabolized by CYP isoenzyme pathways and are potentially safer alternatives in patients receiving concomitant amiodarone.[20,21] Pharmacokinetic data have demonstrated that while amiodarone increases serum simvastatin levels, it does not significantly alter pravastatin's concentrations.[22]

There is only 1 case report of a patient whose aminotransferase values increased after concomitant use of amiodarone and rosuvastatin, which suggests that the potential for an interaction between these agents may exist.[23] Aminotransferase values are generally followed in clinical practice as surrogate markers for liver function, and elevations serve as possible indicators of hepatotoxicity but are not suggestive for muscle side effects as is the case with elevated creatine kinase.[1] To date, there are no published reports of rhabdomyolysis or myopathy with the combination of rosuvastatin and amiodarone. Furthermore, the package inserts of pravastatin and rosuvastatin have no warnings or dose limits regarding their concomitant use with amiodarone.[20,21]

In contrast to rosuvastatin and pravastatin, the other available statins, lovastatin, atorvastatin, and fluvastatin, are extensively metabolized by CYP enzymes.[24-26] Lovastatin's product label warns of an interaction with concomitant amiodarone therapy and stipulates a dose limit of 40 mg per day.[24] Given the possible safety concerns with concomitant amiodarone use, lovastatin was not considered as an alternative to simvastatin in our conversion protocol. Atorvastatin was also not considered as an alternative to simvastatin because of its extensive CYP3A4 metabolism and warning in amiodarone's package insert regarding myopathy and rhabdomyolysis when used concomitantly with atorvastatin or simvastatin.[19,25] In addition, a review of adverse events reported to the FDA demonstrated no statistically significant difference in statin-related adverse events with simvastatin versus atorvastatin in patients receiving concomitant amiodarone.[27] The same review highlighted a significantly lower adverse event rate with pravastatin versus simvastatin when used concomitantly with amiodarone, further emphasizing that pravastatin is potentially the safest statin in combination with amiodarone.[27] Finally, although fluvastatin is apparently the safest statin when used alone,[14] it was not considered as a therapeutic alternative to simvastatin in the conversion protocol because fluvastatin undergoes significant CYP2C9 metabolism and concomitant use with amiodarone could result in higher serum fluvastatin levels.[12,26] And, at the

time of this intervention, fluvastatin was the most expensive nonformulary agent at our institution.

Given the available evidence and lack of CYP-mediated interaction, pravastatin appears to be the potentially safest statin in amiodarone-treated patients. However, for patients taking amiodarone who require more potent LDL-C lowering than is provided by pravastatin, rosuvastatin may be the next preferred statin.[28]

The West Palm Beach VA Medical Center (WPB VAMC) undertook a patient safety initiative for concomitant use of amiodarone and simvastatin at doses greater than 20 mg per day. First, we identified the incidence of the combination of amiodarone and simvastatin in doses greater than 20 mg per day and the prevalence of additional risk factors for myopathy in this population. Second, a protocol for the conversion from simvastatin to pravastatin or rosuvastatin was designed, approved by the local Medication Use (pharmacy and therapeutics) committee, and implemented with the goal of maintaining target LDL-C lowering after statin conversion.

Methods

A report was generated using electronic outpatient pharmacy records from the WPB VAMC on November 1, 2008, to identify all patients with an active prescription for simvastatin at a daily dose greater than 20 mg and a subset of patients with a concomitant prescription for amiodarone. Once identified, the electronic medical record (EMR) for each patient was reviewed by investigator Karimi to determine the dates of concomitant use of amiodarone and simvastatin at doses greater than 20 mg per day. This time frame began on the date the patient initially received amiodarone and simvastatin at a dose greater than 20 mg per day as noted in the electronic pharmacy record and ended on the date of the database search (November 1, 2008). Following this step, the EMRs were individually reviewed by a single author (Karimi) for the entire duration of each patient's use of concomitant amiodarone and simvastatin in doses greater than 20 mg per day to collect the indications for statin use, patient demographics (age and gender), duration of combination therapy, and current risk factors for myopathy (Table 1).[1,11,14] This review occurred immediately after the search of electronic pharmacy records and took place independent of and prior to statin conversion. Demographic information and laboratory data pre-conversion were determined by review of EMR with the most recent values included in the present study.

The risk factors for myopathy that were selected for the present study are outlined in the joint statement from ACC/AHA/NHLBI on the safety of statins.[1] The only risk factors used in the present study that are not specifically mentioned in the ACC/AHA/NHLBI statement are hypothyroidism, diltiazem use, and hepatic insufficiency. Hypothyroidism is mentioned in the ACC/AHA/NHLBI statement as a predisposing factor for myopathy and has been confirmed as a risk factor by other authors.[14] Similarly, concomitant diltiazem use and hepatic insufficiency have been cited in reviews of statin-associated myopathy and were included in our risk factor review.[11] Body mass index was calculated as weight in kilograms divided by height in squared meters (kg/m2).[29] Renal function was determined by Cockcroft-Gault estimation for creatinine clearance with age, weight, and serum creatinine values defined by values recorded nearest to the date of the search of pharmacy records for concomitant therapy.[30] The presence of hypothyroidism was determined by documentation in the EMR problem list, primary care provider documentation in progress notes, or elevated thyroid stimulating hormone ([TSH] >4.8 milli-international units per liter [mIU per L]) and/or decreased free T4 (<0.6 micrograms per deciliter [mcg per dL]) when appropriate (i.e., central hypothyroidism). A diagnosis of diabetes was based on documentation in the EMR problem list, primary care provider documentation in progress notes, or use of medications to treat diabetes. Hepatic insufficiency was determined by problem list documentation and verified by presence of Child-Pugh Classification greater than or equal to 7.[31] Alcohol abuse was determined by documented diagnosis, positive Alcohol Use Disorders Identification Test (AUDIT-C) score, or 2+ score on the "cut-annoyed-guilty-eye" (CAGE) questionnaire.[32,33] The use of medications that may increase the risk of myopathy was recorded from examination of active orders in the electronic pharmacy records during the period of concomitant use of amiodarone with simvastatin in doses greater than 20 mg per day. Each interacting medication identified represented an independent risk factor and was counted only once regardless of the number of times dispensed. For example, for a patient with 2 separate macrolide courses and verapamil use, 2 risk factors were recorded.

Conversion Process

A clinical pharmacist reviewed each patient's chart for potential conversion from simvastatin to an alternative statin using a protocol approved by the WPB VAMC Medication Use Committee. This process was independent of the review for additional risk factors for myopathy. Exclusions from conversion per protocol included patients who were found to no longer be on amiodarone and simvastatin at a dose greater than 20 mg per day and those with a previous adverse drug reaction to either pravastatin or rosuvastatin. Patients on simvastatin 40 mg per day were converted to pravastatin 80 mg per day if they were 10% or more below their LDL-C target at baseline. Otherwise, they were converted to rosuvastatin 5 to 10 mg per day based on renal function; patients whose creatinine clearance was less than 30 milliliters (mL) per minute and who were not on hemodialysis were converted to rosuvastatin 5 mg per day. Patients on simvastatin 80 mg per day at baseline were converted to rosuvastatin 5 mg or 10 mg per day based on renal

function as noted above. Although the daily dose of simvastatin could have been reduced to 20 mg or less, as was done in the SEARCH trial, the conversion protocol was designed to convert patients to high-dose pravastatin or low-dose rosuvastatin in an attempt to maintain an LDL-C lowering effect that was equivalent to that of the higher doses of simvastatin (40 to 80 mg) that the patients were receiving.[17] Patients were mailed a letter informing them of the conversion and the need for follow-up laboratory tests, including LDL-C, high-density lipoprotein cholesterol (HDL-C), triglycerides, total cholesterol, and alanine and aspartate aminotransferases (ALT and AST, respectively). Laboratory tests were scheduled 8 to 12 weeks after the conversion and were reviewed by a clinical pharmacist.

Outcome Measures and Data Analysis

Baseline lipid and aminotransferase values were defined as the most recent, single, laboratory values prior to statin conversion. There were no time limits set for the inclusion of pre-conversion laboratory values as long as they were drawn when the patient was taking the same simvastatin dose as at the time of statin conversion. Creatine kinase values are not routinely assessed in the normal course of clinical practice at our facility and were not available for analysis as part of this conversion.

Paired t-tests with an alpha of 0.05 were used to evaluate changes in lipid and aminotransferase values. Patients without follow-up laboratory tests were excluded from the statistical analysis. Descriptive statistics were used to assess patients' risk factors for myopathy. The paired t-tests were performed using Excel (Microsoft Corporation, Redmond, WA).

Results

Conversion Process

Of the 92 patients identified on the combination of amiodarone and simvastatin in doses greater than 20 mg per day, 76 (82.6%) were converted per protocol and 62 (67.4%) had follow-up lipid and amiotransferase data available. Of these 62 patients, 55 (88.7%) were converted to rosuvastatin 5 mg (n = 5) or rosuvastatin 10 mg (n = 50), and 7 (11.3%) were converted to pravastatin 80 mg per day (Figure 1). Following conversion, the mean (SD) time to laboratory testing was 11.9 (5.6) weeks (median [interquartile range] of 9.7 [8.6-14.9] weeks). There were no statistically significant differences in mean lipid or aminotransferase values from baseline to follow-up for the 62 patients who underwent statin conversion and who had follow-up laboratory values available (Figures 2 and 3). Specifically, mean LDL-C was 71 mg per dL prior to conversion and 67 mg per dL after conversion ($P = 0.119$) in those patients with follow-up laboratory values available.

After clinical pharmacist review of follow-up lipid values, 4 of 50 (8.0%) patients who had been converted to rosuvastatin 10 mg per day required dose titration to 20 mg per day. One patient was taken off rosuvastatin 10 mg per day and subsequently converted to pravastatin 20 mg per day by the patient's primary care physican due to complaints of myalgia ("leg pain" in the primary care notes), which occurred approximately 3 months after the conversion. Neither a creatine kinase nor TSH level was obtained at the time of the complaint of mylagia. However, the patient's symptoms resolved with discontinuation of rosuvastatin and substitution of pravastatin. After conversion to pravastatin, repeat LDL-C values remained below primary LDL-C target (< 100 mg per dL) for this patient with CAD.

Sixteen patients were not converted according to the conversion protocol because amiodarone was discontinued (n = 4), statin therapy was discontinued (n = 2), the simvastatin dose was reduced to no more than 20 mg per day (n = 6), or the patient was converted to an alternative statin regimen (n = 4).

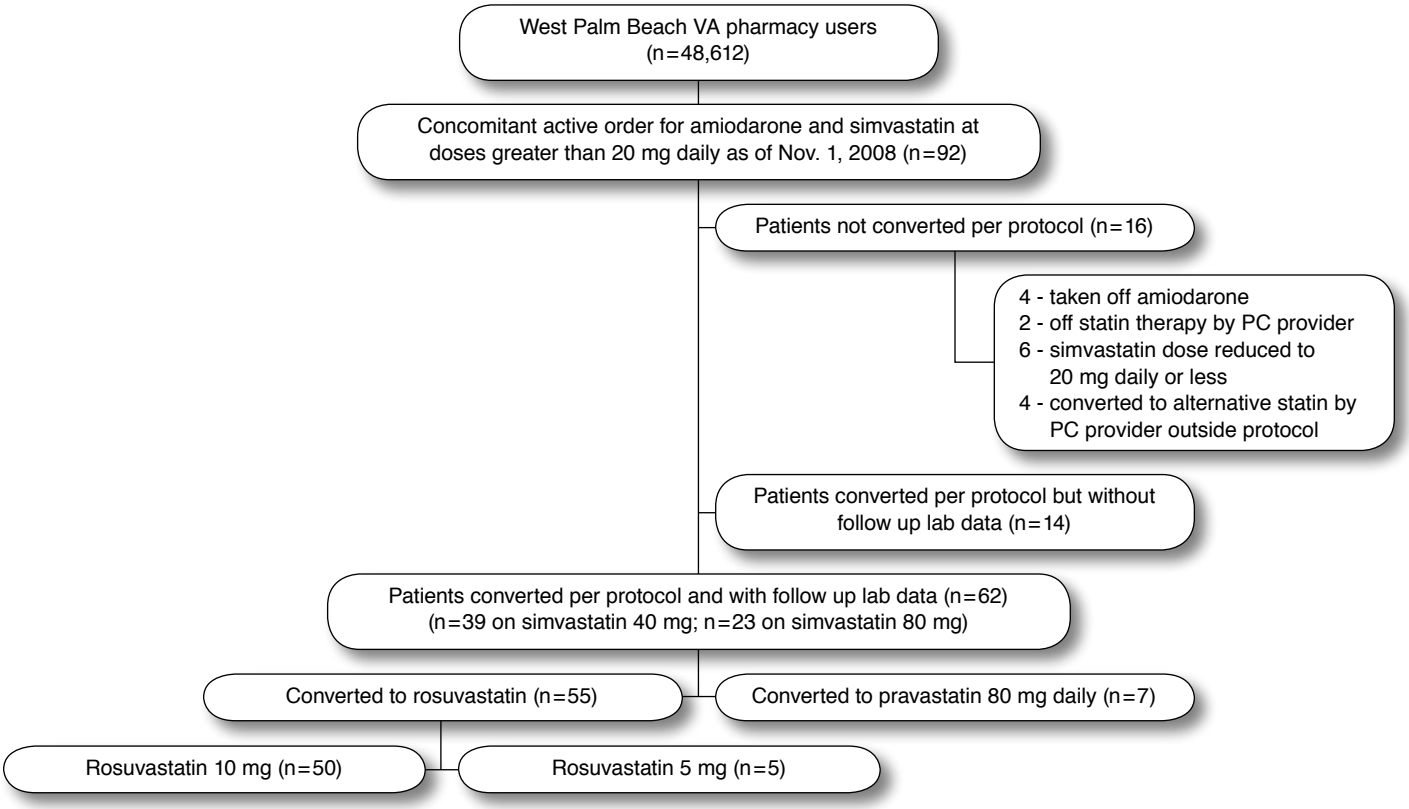
Risk Factor Assessment

All 92 patients originally on the combination of amiodarone and simvastatin in doses greater than 20 mg per day were included in the myopathy risk factor assessment. These 92 patients represented 0.19% of 48,612 unique patients with active outpatient pharmacy orders for any drug and 0.52% of 17,760 unique patients on simvastatin at doses greater than 20 mg per day. Nearly all (91 of 92) patients were male, the mean age was 78 years, and 95.7% had CAD and therefore a compelling indication for statin therapy (Table 1). The mean duration of therapy with amiodarone and simvastatin in doses greater than 20 mg per day was 43 months with a median (interquartile range) of 37 months (19-67 months). Additional risk factors for myopathy are detailed in Table 1 with 26 (28.3%), 35 (38.0%), and 18 (19.6%) patients having 1, 2, or 3 or more additional risk factors for myopathy, respectively. Conversely, there were no additional risk factors, other than concomitant simvastatin and amiodarone therapy, in 13 (14.1%) patients.

Discussion

The prevalence of amiodarone and simvastatin in doses greater than 20 mg per day was relatively low as a proportion of the total number of patients who utilize the WPB VA pharmacy. Only the concomitant prevalence of amiodarone with simvastatin at daily doses greater than 20 mg based on simvastatin patient volume allows for comparison to other work. Our finding of 0.52% of simvastatin 40 mg or 80 mg daily users having concurrent amiodarone use is less than the 1.6% previously reported in a review using 2006 data from the national SDI Vector One database, which includes data from more than 2 billion claims annually from "national retail chains, mail order pharmacies, mass merchandisers, pharmacy benefits managers and their data systems, and provider groups."[34] The lower concurrency rate in our population may represent changes in provider prescribing habits in response to the FDA warning given that our review used data from late 2008. Also, the

FIGURE 1 Flowchart for Patient Selection and Statin Conversion[a]



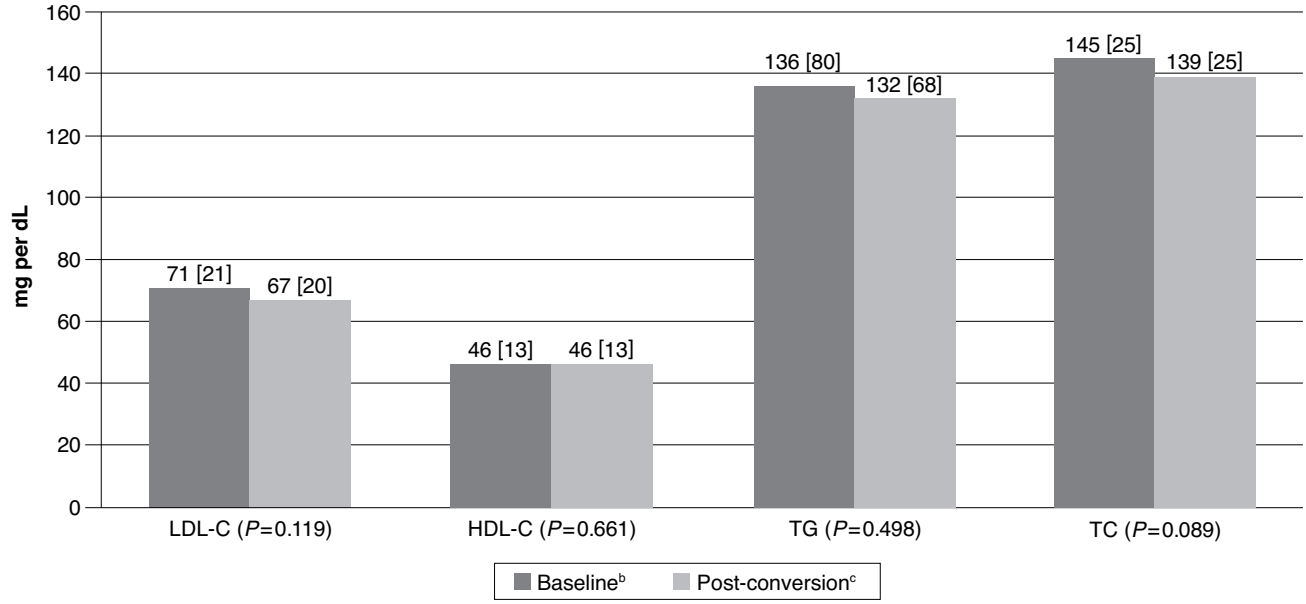
[a]*Electronic pharmacy record search performed on November 1, 2008, to identify patients with active orders for both amiodarone and simvastatin in doses greater than 20 mg per day. All patients identified were included in the risk factor analysis. Those patients converted per protocol were converted from simvastatin to either pravastatin or rosuvastatin based on baseline simvastatin dose and LDL-C value. Those on simvastatin 40 mg daily were converted to pravastatin 80 mg daily if the baseline LDL-C value was more than 10% below the LDL-C target. If patients were less than 10% below the LDL-C target or above at baseline, they were converted to rosuvastatin 10 mg daily (5 mg if CrCl <30 mL per minute and not on hemodialysis). Those on simvastatin 80 mg daily were converted to rosuvastatin 10 mg daily (5 mg daily if CrCl <30mg per dL and not on hemodialysis).*

CrCl = creatinine clearance; dL = deciliter; LDL-C = low-density lipoprotein cholesterol; mg = milligrams; mL = milliliter; PC = primary care; VA = Department of Veterans Affairs.

relative difference in concurrency may be a result of studying 2 different populations because the 2006 review included more than 160 million unique patents nationwide and our review included 48,612 pharmacy users at a single VA site.[34]

The present study revealed that 79 (85.9%) patients on the combination of amiodarone and simvastatin in doses greater than 20 mg per day at our institution had at least 1 additional risk factor for myopathy or rhabdomyolysis during their history of combination therapy. No other study that we are aware of has assessed additional risk factors for myopathy in patients who have received amiodarone concomitantly with more than 20 mg simvastatin per day. Of the risk factors that were assessed, older age (>80 years) was the most common (43.5%), followed by diabetes (35.9%), and hypothyroidism had an unusually high prevalence (31.5%). The prevalence of hypothyroidism can be affected by many factors and varies among published data. According to the National Health and Nutrition Examination Survey (NHANES) of 1999-2002, the prevalence of hypothyroidism in the United States is reportedly 3.7%.[35] Given that we are evaluating older patients receiving amiodarone therapy (which has propensity to cause thyroid abnormalities independently at rates of 2%-10% for hypothyroidism and approximately 2% for hyperthyroidism), it is not surprising that the prevalence of hypothyroidism in our patients is greater compared with the general population.[35] Although the presence of additional risk factors for myopathy did not alter the need for, or immediacy of, conversion from high doses of simvastatin to pravastatin or rosuvastatin, we collected data on the presence of these alternative risk factors to better characterize the types of risks of myopathy present in

FIGURE 2 Mean [SD] Lipid Values Before and After Statin Conversion (n = 62)[a]



[a]*Of 92 patients who received the combination of amiodarone and simvastatin more than 20 mg per day, 16 were not converted to an alternate statin and 14 did not have post-conversion lipid values available.*

[b]*The baseline values are those closest in time prior to statin conversion for the simvastatin dose at the time of conversion.*

[c]*Post-conversion values were measured from the conversion date through end of data collection in July 2009; the mean (median) time for follow-up laboratory values was 11.9 (9.7) weeks post-conversion (interquartile range = 8.6-14.9 weeks). P values for paired t-test, comparing baseline with post-conversion values for the 62 patients with observations in both time periods.*

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; mg per dL = milligrams per deciliter; SD = standard deviation; TC = total cholesterol; TG = triglycerides.

our patients and to underscore the need for providers to assess these risks when prescribing medications that may increase a patient's risk for myopathy.

In the 62 patients (67.4%) who were converted per protocol from simvastatin at doses greater than 20 mg per day to either pravastatin or rosuvastatin and who had follow-up laboratory values, LDL-C lowering was maintained without significant changes in other lipid or aminotransferase values. Although 1 patient reported myalgia after conversion to rosuvastatin, the reaction appeared minor, as detailed in the patient's chart by the primary care physician, and was not confirmed with objective data (e.g., no creatine kinase value) or rechallenge.

As previously discussed, pravastatin, which lacks CYP450 metabolism, is probably the safest statin to use with concomitant amiodarone.[20] However, given the limited LDL-C lowering potency of pravastatin, rosuvastatin was utilized in the majority of study patients.[28] Although not yet available in the United States, pitavastatin, which has potency similar to that of rosuvastatin and only minimal CYP2C9 and 3A4 metabolism, may be an option in the future for patients who are on amiodarone therapy and require more potent LDL-C lowering. However, pharmacokinetic and safety data should be assessed to verify this assertion.[36,37]

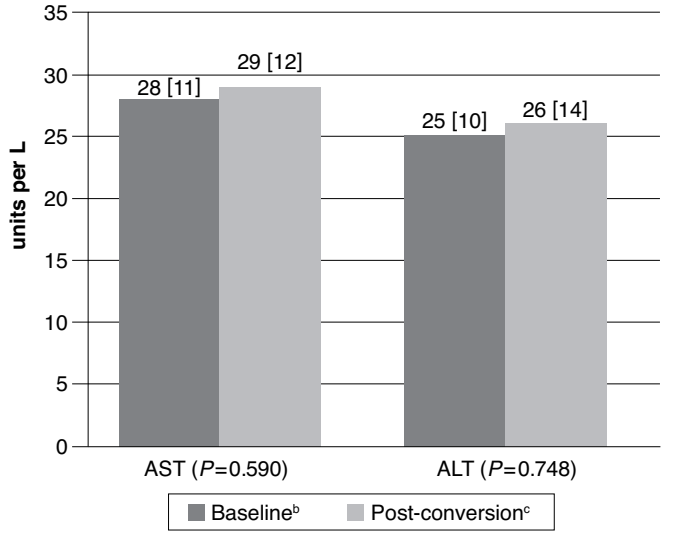
Future investigations may provide additional information on the association between the risk of myopathy and pharmacogenomics. A secondary analysis of the SEARCH data demonstrated that the risk of myopathy was increased in patients with at least 1 common variant in the SLCO1B1 gene, encoding the organic anion-transporter OAT1B1 that mediates hepatic uptake of various statins.[16] Although currently not part of clinical practice, these findings emphasize the potential importance of avoiding concomitant use of statins with other medications that may increase myopathy risk, especially in patients who have genetic variants that may increase serum statin levels in addition to established risk factors for myopathy.

In addition to converting patients who were being treated with both amiodarone and simvastatin in doses greater than 20 mg per day to alternative statins, our institution implemented mechanisms to emphasize this interaction in our electronic pharmacy order entry system. A drug file message was created to notify prescribers that simvastatin doses greater than 20 mg per day should not be used in patients on concomitant

amiodarone when prescribers are entering electronic orders for simvastatin in doses of 40 mg or 80 mg. If a prescriber bypasses the drug file message and enters an order for simvastatin 40 mg or 80 mg per day for a patient already on amiodarone, or vice versa, the pharmacist will contact the prescriber either directly (phone or email) or through a "flag" (brief electronic correspondence) in the electronic order entry system regarding the need to convert the patient to a potentially safer statin. In an editorial by Curtiss and Fairman, the appropriate use of prescriber alerts was discussed as a potentially important step in the "mission" of preventing adverse drug reactions.[38] Given the serious potential consequences of rhabdomyolysis, it seems reasonable that the "noise" generated by this alert is outweighed by the potential benefit it offers. Also, the alert, or "flag," that is generated by the pharmacy and sent to the ordering prescriber offers the opportunity to convey information about the interaction directly along with recommendations for alternative statins.

In March 2010, an additional communication from the FDA was distributed regarding the ongoing safety review of high-dose simvastatin (80 mg per day) and the increased risk of muscle injury. This communication recommended that health care professionals be aware that, although rhabdomyolysis is a rare event experienced with all statins, there is a potential for drug-drug interactions and the increased risk of myopathy.[39] This FDA update again warned that amiodarone should not be used in combination with more than 20 mg of simvastatin per day. There appears to be a continuing need for health care systems to take action to decrease patient exposure to the combination of amiodarone and high-dose simvastatin and to convert amiodarone-treated patients to potentially safer statins if more than 20 mg per day of simvastatin is necessary to attain lipid goals.

TABLE 3 Mean [SD] Aminotransferase Values Before and After Statin Conversion (n = 62)[a]



[a]Of 92 patients who received the combination of amiodarone and simvastatin more than 20 mg per day, 16 were not converted to an alternate statin and 14 did not have post-conversion lipid values available.

[b]The baseline values are those closest in time prior to statin conversion for the simvastatin dose at the time of conversion.

[c]Post-conversion values were measured from the conversion date through end of data collection in July 2009; the mean (median) time for follow-up laboratory values was 11.9 (9.7) weeks post-conversion (interquartile range=8.6-14.9 weeks).

P values for paired t-test, comparing baseline with post-conversion values for the 62 patients with observations in both time periods.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; L = liter; SD = standard deviation.

Limitations

Among the limitations of the present study was the use of a nonrandomized, paired group design that did not specify the minimum and maximum time periods for inclusion of baseline and post-conversion lipid and aminotransferase values. Therefore, it is possible that any differences in these lipid and aminotransferase levels could be attributed to reasons other than the statin that these patients received. Second, because this intervention included mainly older, male veterans, the results may not be generalizable to other patient populations. However, since the final selection of an alternative statin was based on LDL-C lowering potential, which has been examined across various populations, it would be reasonable to expect similar lipid and aminotransferase outcomes in other groups and health care settings.[28] Third, this study did not call for laboratory values for creatine kinase, myoglobin, or TSH at baseline or follow-up, thereby limiting evaluation of potential safety concerns and preventing evaluation of the complaint of mylagia that was reported in 1 patient converted to rosuvastatin. Fourth, we did not specify a threshold for change in aminotransferase values that might have helped to identify potential safety concerns after conversion.

Fifth, retrospective review of EMRs to assess risk factors for myopathy is limited by the accuracy of information recorded in EMRs and pharmacy records. For example, it was difficult to ascertain whether patients who were on the combination of amiodarone, simvastatin, and an interacting azole or macrolide, had their simvastatin withheld during the duration of antibiotic therapy. In addition, patients may have received medications from outside the study medical facility that increase the risk of myopathy of which we were not aware. Finally, a positive AUDIT-C score is an indicator but not necessarily diagnostic for alcohol abuse (e.g., as few as 3 drinks per week for females and 4 drinks per week for males produce a positive AUDIT-C score), and may overestimate alcohol abuse.[32] In the present study, 17.4% of patients had at least 1

positive AUDIT-C score, but no patients were receiving active treatment for alcohol abuse.

Conclusion

Less than 1% of patients who had pharmacy records in this VA medical center in 2008 were on a dose of simvastatin greater than 20 mg per day with concomitant amiodarone therapy, but a majority of patients on this combination had additional risk factors for myopathy. Although this study did not assess patient complaints of muscle pain or more serious myopathy, there appears to be a continuing need to monitor the concomitant use of these 2 drugs. Patients in this study who were converted to either pravastatin or rosuvastatin maintained therapeutic goal for LDL-C lowering, without a significant change in mean aminotransferase levels and 1 reported case of mylagia with rosuvastatin. As a result of this study and intervention, edits were incorporated into the EMR to prevent the use of amiodarone with simvastatin in doses greater than 20 mg per day.

Authors

SAHAR KARIMI, PharmD, is a Clinical Pharmacy Specialist in Primary Care, Kaiser Permanente, Manassas and Reston, Virginia. AUGUSTUS HOUGH, PharmD, is a Clinical Pharmacy Specialist in Primary Care; and CHERYLYN BECKEY, PharmD, BCPS, CDE, is a Clinical Pharmacy Specialist in Pharmacoeconomics, West Palm Beach Veterans Affairs Medical Center, West Palm Beach, Florida. DAVID PARRA, PharmD, FCCP, BCPS, is a Clinical Pharmacy Specialist in Cardiology, West Palm Beach Veterans Affairs Medical Center, West Palm Beach, Florida, and Clinical Assistant Professor, Department of Experimental and Clinical Pharmacology, University of Minnesota College of Pharmacy.

AUTHOR CORRESPONDENCE: Augustus Hough, PharmD, West Palm Beach VA Medical Center, 7305 N. Military Trail, West Palm Beach, FL 33410. Tel.: 561.422.7625; Fax: 561.422.7213; E-mail: augustus.hough@va.gov.

DISCLOSURES

The authors report no financial or other conflicts of interest related to the subject of this article. The views in this article reflect those of the authors and not necessarily those of the Department of Veterans Affairs. Portions of the results of this safety initiative were presented as a poster at the American College of Clinical Pharmacy Annual Meeting, Anaheim, California, October 18-21, 2009.

Beckey, Karimi, and Parra created the study concept and design. Karimi and Hough collected and interpreted the data. Karimi with the assistance of the other authors wrote the manuscript, and Hough with the assistance of the other authors revised the manuscript.

ACKNOWLEDGEMENT

The authors thank Marisel S. Segarra-Newnham, PharmD, MPH, FCCP, BCPS, for her guidance in the design and implementation of this project.

REFERENCES

1. Pasternak RC, Smith SC, Bairey-Merz CN, Grundy SM, Cleeman JI, Lenfant C. ACC/AHA/NHLBI Clinical advisory on the use of and safety of statins. *Circulation*. 2002;106(8):1024-28. Available at: http://circ.ahajournals.org/cgi/reprint/106/8/1024. Accessed August 2, 2010.

2. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360(9326):7-22.

3. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA*. 1998;279(20):1615-22. Available at: http://jama.ama-assn.org/cgi/reprint/279/20/1615. Accessed August 2, 2010.

4. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med*. 1995;333:1301-07. Available at: http://content.nejm.org/cgi/reprint/333/20/1301.pdf. Accessed August 2, 2010.

5. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med*. 1996;335(14):1001-09. Available at: http://content.nejm.org/cgi/reprint/335/14/1001.pdf. Accessed August 2, 2010.

6. LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. *JAMA*. 1999;282(24):2340-46. Available at: http://jama.ama-assn.org/cgi/reprint/282/24/2340. Accessed August 2, 2010.

7. No authors listed. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344(8934):1383-89.

8. No authors listed. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. *N Engl J Med*. 1998;339(19):1349-57. Available at: http://content.nejm.org/cgi/reprint/339/19/1349.pdf. Accessed August 2, 2010.

9. Joy TR, Hegele RA. Narrative review: statin-related myopathy. *Ann Intern Med*. 2009;150(12):858-68. Available at: http://www.annals.org/content/150/12/858.full.pdf+html. Accessed August 2, 2010.

10. Kashani A, Phillips CO, Foody JM, et al. Risks associated with statin therapy: a systematic overview of randomized clinical trials. *Circulation*. 2006;114(25):2788-97. Available at: http://circ.ahajournals.org/cgi/reprint/114/25/2788. Accessed August 2, 2010.

11. Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. *JAMA*. 2003;289(13):1681-90.

12. Jacobson TA. Toward "Pain-Free" statin prescribing: clinical algorithm for diagnosis and management of myalgia. *Mayo Clin Proc*. 2008;83(6):687-700. Available at: http://www.mayoclinicproceedings.com/content/83/6/687.full.pdf+html. Accessed August 2, 2010.

13. Davidson MH, Clark JA, Glass LM, Kanumalla A. Statin safety: an appraisal from the adverse event reporting system. *Am J Cardiol*. 2006;97(8A):32C-43C.

14. Ballantyne CM, Corsini A, Davidson MH, et al. Risk for myopathy with statin therapy in high-risk patients. *Arch Intern Med*. 2003;163(13):553-64. Available at: http://archinte.ama-assn.org/cgi/reprint/163/5/553. Accessed August 2, 2010.

15. U.S. Food and Drug Administration. Interaction between amiodarone (marketed as Cordarone and Pacerone) and simvastatin (marketed as Zocor and generics) or simvastatin-combination products (marketed as Vytorin and Simcor). *Drug Safety Newsletter*. 2008;1(4):46-48. Available at: www.fda.gov/downloads/Drugs/DrugSafety/DrugSafetyNewsletter/ucm109178.pdf. Accessed August 2, 2010.

16. SEARCH Collaborative Group, Link E, Parish S, Armitage J, et al. SLCO1B1 variants and statin-induced myopathy—a genomewide study. *N Engl Med*. 2008;359(8):789-99. Available at: http://content.nejm.org/cgi/reprint/359/8/789.pdf. Accessed August 2, 2010.

17. Search Study Collaborative Group, Bowman L, Armitage J, Bulbulia R, Parish S, Collins R. Study of the effectiveness of additional reductions in cholesterol and homocysteine (SEARCH): characteristics of a randomized trial among 12064 myocardial infarction survivors. *Am Heart J*. 2007;154(5):815-23. Available at study website (trial-related documents, SEARCH baseline paper) at: www.searchinfo.org. Accessed August 2, 2010.

18. Bellosta S, Paoletti R, Corsini A. Safety of statins. Focus on clinical pharmacokinetics and drug interactions. *Circulation*. 2004:109(23 suppl):50-57. Available at: http://circ.ahajournals.org/cgi/reprint/109/23_suppl_1/III-50. Accessed August 2, 2010.

19. Pacerone (amiodarone HCl) tablets, 100 mg and 200 mg. Upsher-Smith. October 2009. Available at: http://www.upsher-smith.com/PDFs/Pacerone_PI.pdf. Accessed August 2, 2010.

20. Pravachol (pravastatin sodium) tablets. Bristol-Myers Squibb Company. March 2007. Available at: http://packageinserts.bms.com/pi/pi_pravachol.pdf. Accessed August 2, 2010.

21. Crestor (rosuvastatin calcium). AstraZeneca Pharmaceuticals LP. June 2010. Available at: http://www1.astrazeneca-us.com/pi/crestor.pdf. Accessed August 2, 2010.

22. Becquemont L, Neuvonen M, Verstuyft C, et al. Amiodarone interacts with simvastatin but not with pravastatin disposition kinetics. *Clin Pharmacol Ther*. 2007;81(5):679-84.

23. Merz T, Fuller SH. Elevated serum transaminase levels resulting from concomitant use of rosuvastatin and amiodarone. *Am J Health Syst Pharm*. 2007;64(17):1818-21.

24. Mevacor (lovastatin). Merck & Co, Inc. May 2010. Available at: http://www.merck.com/product/usa/pi_circulars/m/mevacor/mevacor_pi.pdf. Accessed August 2, 2010.

25. Lipitor (atorvastatin calcium) tablets. Pfizer Ireland Pharmaceuticals. June 2009. Available at: http://www.pfizer.com/files/products/uspi_lipitor.pdf. Accessed March 28, 2010.

26. Lescol (fluvastatin sodium) capsules. Novartis. October 2006. Available at: http://www.pharma.us.novartis.com/product/pi/pdf/Lescol.pdf. Accessed August 2, 2010.

27. Alsheikh-Ali AA, Karas RH. Adverse events with concomitant amiodarone and statin therapy. *Prev Cardiol*. 2005;8(2):95-97.

28. Jones PH, Davidson MH, Stein EA, et al.; STELLAR Study Group. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin and pravastatin across doses (STELLAR* Trial). *Am J Cardiol*. 2003;92(2):152-60.

29. World Health Organization. Global strategy on diet, physical activity and health: obesity and overweight. 2003. Available at: www.who.int/dietphysicalactivity/publications/facts/obesity/en/. Accessed August 2, 2010.

30. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. *Am J Kidney Dis*. 2002;39:S1-S26. Available at: http://www.kidney.org/professionals/kdoqi/pdf/ckd_evaluation_classification_stratification.pdf. Accessed August 2, 2010.

31. Child-Turcotte-Pugh score – classification of liver dysfunction. Available at: http://www.globalrph.com/child_pugh.htm. Accessed August 2, 2010.

32. Saunders JB, Aasland OG, Babor TF, de la Fuente JR, Grant M. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption--II. *Addiction*. 1993;88(6):791-804.

33. Mayfield D, McLeod G, Hall P. The CAGE questionnaire: Validation of a new alcoholism screening instrument. *Am J Psychiatry*. 1974;131(10):1121-23.

34. Borders-Hemphill V. Concurrent use of statins and amiodarone. *Consult Pharm*. 2009;24(5):372-79.

35. Aoki Y, Belin RM, Clickner R, Jeffries R, Phillips L, Mahaffey KR. Serum TSH and total T4 in the United States population and their association with participant characteristics: National Health and Nutrition Examination Survey (NHANES 1999-2002). *Thyroid*. 2007;17(12):1211-23.

36. Hayashi T, Yokote K, Saito Y, Iguchi A. Pitavastatin: efficacy and safety in intensive lipid lowering. *Expert Opin Pharmacother*. 2007;8(14):2315-27.

37. Mukhtar RY, Reid J, Reckless JP. Pitavastatin. *Int J Clin Pract*. 2005;59(2):239-52.

38. Curtiss FR, Fairman KA. Quality improvement opportunities in prescriber alert programs. *J Manag Care Pharm*. 2010;16(4):292-96. Available at: http://www.amcp.org/data/jmcp/292-296.pdf.

39. U.S. Food and Drug Administration. FDA Drug Safety Communication: Ongoing safety review of high-dose Zocor (simvastatin) and increased risk of muscle injury. March 19, 2010. Available at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm204882.htm#AdditionalInformationforHealthcareProfessionals2. Accessed August 2, 2010.