Lipid Profile Changes Associated With Changing Available Formulary Statins: Removing Higher Potency Agents

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Objective: To review the fasting lipid panel changes that occurred after removing higher potency statins from a prescription formulary.

Study Design: Retrospective chart review.

Methods: Researchers compiled data for patients in a medical clinic receiving pharmacy benefits from a particular managed care plan. Patients enrolled in the benefits program at least between June 2006 and June 2007 were evaluated for atorvastatin use before January 1, 2007. After January 1, patients on atorvastatin were prescribed new statins according to the program's preferred drug list. Patients treated with atorvastatin were reviewed for fasting lipid panel results while on atorvastatin; these results then were compared with fasting lipid panels after the formulary change took place. Total cholesterol, low-density lipoprotein, high-density lipoprotein, and triglyceride values were examined for changes. Appropriateness of the replacement statin also was evaluated using statin equivalency charts.

Results: Values for total cholesterol, low-density lipoprotein, and triglycerides were not significantly different from baseline to follow-up. High-density lipoprotein values did significantly increase over the study period. Only 34% of statin prescriptions were considered appropriately converted to equipotent or higher potency doses. The mean time to documentation of statin conversion was 2.9 months.

Conclusions: Removing higher potency statins from the formulary did not significantly change a population's fasting lipid panel except for a significant increase in high-density lipoprotein. Although multiple factors may have contributed to this effect, the results of this investigation suggest that changing formulary statins will not alter the surrogate lipoprotein markers associated with poor cardiovascular outcomes.

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For author information and disclosures, see end of text.

Spending in the United States for prescription drugs was $216.7 billion in 2006, and it has been one of the fastest growing components of the healthcare budget.[1] In an effort to provide comprehensive healthcare services while trying to decrease the rising costs of prescription drugs to society, managed care plans and most third-party payers have instituted formularies to help control the utilization of pharmaceuticals within their respective plans. Formularies, limited lists of approved pharmaceuticals, are the most prevalent means of containing drug costs and are utilized by most managed care plans.[2] Health Maintenance Organizations, Preferred Provider Organizations, and some traditional plans use the strategy of offering lower copayments for formulary generic medications and increasing costs more than 3 times higher for a brand name drug not on the formulary.[3]

In 2007, approximately 13 million persons were treated with atorvastatin, accounting for $6.16 billion in sales. Although the dollar amount has remained relatively unchanged over the last 5 years, third-party payers and managed care plans continue to look for ways to decrease cost.[4,5] This is commonly done by selecting several preferred cheaper generic substitutions and/or brand name options that are then included on the company's prescription drug formulary. A managed care plan's formulary selection affects many aspects of care, including the provider's choice of medication and the patient's satisfaction with therapy, as well as the patient's adherence to lipid-lowering therapy.[6,7] The development of a medication formulary gives these third-party payers a cost-effective way to provide quality care. When a generic and/or preferred option is chosen, both patients and payers benefit. Adhering to a formulary will decrease cost to payers, resulting in discounted pricing for the patient.[7] Also, research has shown that when patients are prescribed medications included on their prescription insurance formulary, their likelihood of remaining adherent to the medication regimen is increased.[8]

Although patients may remain adherent to the medication regimen, these drugs are selected on the basis of average patient outcome, not individual effectiveness.[2] It is important that managed care plans be careful to not compromise individual patient health when decreasing the cost of prescription drugs. In the case of prescription formularies, limiting access to higher potency statins may affect a patient's and a provider's ability to reach therapeutic fasting lipid panel levels in a reasonable and safe amount of time.[9] In addition, very strict limi-

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The higher potency agents (atorvastatin and rosuvastatin) are available only under their proprietary names, whereas the moderate potency statins (simvastatin, lovastatin, and pravastatin) are more readily available through multiple generic manufacturers.

- Removing higher potency statins from the formulary did not significantly influence a population's fasting lipid panel except for a significant increase in high-density lipoprotein.
- This lack of difference was seen with only 34% of statin prescriptions considered appropriately converted to equipotent or higher potency doses.

tations could hinder patients' access to the medication during a critical point in their therapy such as immediately post–myocardial infarction.[10]

Although most statins may be considered equivalent with regard to primary and secondary prevention of cardiovascular disease, the lipid-lowering potential of each individual statin is based on the agent's potency and dose.[11] These differences can potentially affect patients' ability to reach their fasting lipid panel goals. Since December 2001, 3 of the 6 available statins have been approved in generic formulations, thereby offering a less expensive option for third-party payers and managed care plans.

Multiple clinical trials have demonstrated that changing to a more potent statin is associated with additional low-density lipoprotein (LDL) reduction.[12-16] However, because most of the higher potency statins still are available only under their brand name, their managed care availability may be limited.

When a provider is prompted to change from a nonformulary medication to a formulary medication, the opportunity arises to evaluate the patient's current lipid levels and reassess the appropriateness of statin choice and dose. Miller et al recently found that the "usual care" associated with switching from atorvastatin during a formulary change resulted in a significant increase in LDL, non–high-density lipoprotein (HDL), and total cholesterol.[17] These results imply that the practice of therapeutic statin conversion during a formulary change may need more guidance. Although prescribers may be aware of the potency differences between the available statins, we cannot conclude that they are aware of the necessary dose changes when changing to a different statin. An inappropriate, suboptimal dose change could result in a worsened lipid profile and increased risk for cardiovascular event.

Our objective was to investigate the changes in fasting lipid panels based on individual effectiveness in a population that underwent a similar formulary change and needed statin conversion.

METHODS

This retrospective chart review was conducted with St. Luke's Hospital and Health Network in Bethlehem, Pennsylvania, in an internal medicine primary care clinic. Each patient evaluated underwent a statin conversion after a managed care plan and prescription insurance provider removed atorvastatin from the preferred drug formulary. All information was gathered to ensure patient privacy and the protocol was reviewed and approved (deemed exempt) by the institutional review board of the St. Luke's Hospital and Health Network.

Patients were identified using a member census provided monthly by the managed care plan. Patients were included if they were age 18 years or older and were enrolled in the managed care plan from at least June 2006 to June 2007. Patients who had been enrolled before June 2006 and/or continued beyond June 2007 also were eligible. Finally, patients had to have started taking atorvastatin (Lipitor, Parke-Davis & Pfizer Inc, New York, NY) at any dose prior to June 2006. Patients taking atorvastatin after the formulary change date because of prior authorization approval were included in the analysis.

Patients were excluded if they were not taking atorvastatin prior to June 2006, did not have a baseline lipid panel documented at least 6 weeks after starting the last documented atorvastatin dose, or did not have a follow-up lipid panel documented at least 6 weeks after starting the latest replacement statin dose. Patients also were excluded if they had baseline or follow-up triglycerides greater than 400 mg/dL without a direct LDL value, or if their atorvastatin dose or replacement statin dose was not documented in the medical chart. Patients were not excluded if they were using concurrent nonstatin lipid-lowering agents such as nicotinic acid, fibrates, bile acid sequestrants, or absorption inhibitors.

The primary end point was the observed change in fasting lipid panel components after converting from atorvastatin to another formulary statin. Follow-up assessments used the first fasting lipid panel at least 3 months after the medication change was prescribed. The population also was subdivided and compared as "high risk" patients, requiring LDL cholesterol to be less than 100 mg/dL, and moderate- to low-risk patients, requiring LDL cholesterol to be less than 130 mgdL. As a secondary end point, we evaluated the same criteria used in the primary end point for each baseline atorvastatin dose. In addition, we reviewed the data for appropriateness of the replacement statin based on LDL-lowering potential (**Table 1**).

For this research, appropriateness was defined as being at least equipotent to the last documented atorvastatin dose with regard to LDL-lowering potential. Given that we did not interview or assess the patient for adherence, appropriateness did not include evaluating whether a dose adjustment was needed based

on the baseline fasting lipid panel. If the patient was continued on atorvastatin at the same or greater dose with prior authorization approval, this treatment was considered appropriate. We also evaluated the time elapsed from the date of the formulary change (January 1, 2007) to documented statin change in the patient's medical record. During this time, patients were assumed to be without statin therapy as the pharmacy benefits manager did not offer a formulary change grace period. Changes made during January 2007 were valued as zero months.

Statistical Analysis

All data collection and statistical analyses were performed using Microsoft's Access and Excel (Access 2004 and Excel 2004 for Macintosh; Microsoft Corp, Redmond, WA). The differences in fasting lipid profiles (total cholesterol, LDL, HDL, and triglycerides) from baseline with atorvastatin treatment to follow-up with a replacement statin were evaluated using the *t* test. Appropriateness and mean time to statin change were not evaluated for statistical significance and are reported as descriptive statistics only. All *t* tests were performed using a 2-sided alpha of .05 unless otherwise noted.

RESULTS

Using the managed care program enrollment time frame described in the Methods section, 328 patients were evaluated for inclusion in the study. Of these, 102 patients were actively receiving atorvastatin for primary and secondary prevention of coronary artery disease. Thirty-one patients were excluded from this group for various reasons including triglycerides greater than 400 mg/dL without a direct LDL value, no baseline lipid panel, no follow-up fasting lipid panel, or atorvastatin change not noted in the medical record. A more detailed description is provided in Table 2. Demographics for patients included in the evaluation are reported in Table 3.

After comparing fasting lipid profiles for the primary end point, only HDL levels changed significantly. Average baseline HDL levels were measured as 42.5 mg/dL on atorvastatin compared with 44.4 mg/dL after starting the alternate statin (P = .018). Though slightly improved, changes were not significant for LDL (104.0 mg/dL vs 98.9 mg/dL; P = .417) or triglycerides (145.8 mg/dL vs 142.5 mg/dL; P = .637). Total cholesterol was slightly increased (171.6 mg/dL vs 172.3 mg/dL; P = .885).

Table 1. Statin Equivalency Reference[11,18-22]

	Atorvastatin (Lipitor)			
New Statin (Generic)	**10 mg[a]**	**20 mg**	**40 mg**	**80 mg**
Lovastatin	40 mg[a]	80 mg	—	—
Pravastatin	40 mg[a]	80 mg	—	—
Simvastatin	20 mg[a]	40 mg	80 mg	—

[a]These doses are identified by the National Cholesterol Education Program Adult Treatment Panel III as standard doses.

In the high-risk subgroup (n = 39), 64.1% of patients had an LDL of less than 100 mg/dL while taking atorvastatin at any dose. After the formulary change and statin conversion, 71.8% of patients had an LDL of less than 100 mg/dL. In the moderate- to low-risk subgroup (n = 32), 87.5% of patients had an LDL of less than 130 mg/dL on atorvastatin, which decreased to 81.3% after the formulary change and conversion. Though neither comparison resulted in a statistically significant difference, the small subgroup size did not allow for appropriate power.

For the secondary end point, we chose to evaluate whether changes in lipid panel parameters were significant with respect to specific atorvastatin doses (Table 4). Statistically significant changes were noted only for total cholesterol in patients originally treated with atorvastatin 20 mg (n = 10; 158.9 mg/dL vs 181.9 mg/dL; P = .019) and for triglycerides in patients originally treated with atorvastatin 80 mg (n = 15; 180.5 mg/dL vs 150.1 mg/dL; P = .049). The change in HDL for patients treated with atorvastatin 20 mg trended toward significant (40.0 mg/dL vs 43.8 mg/dL; P = .054), but did not reach statistical significance.

Table 2. Eligible and Enrolled Patients

Patient Information	No.
Eligible for evaluation	328
Not taking atorvastatin (or statin)	226
Patients taking any dose of atorvastatin	102
Dose not documented	5
Triglycerides >400 mg/dL pre-2007 fasting lipid profile	1
Statin change not noted	15
Triglycerides >400 mg/dL post-2007 fasting lipid profile	1
No follow-up fasting lipid profile documentation	9
Patients included in final analysis	71
Atorvastatin 10 mg	22
Atorvastatin 20 mg	10
Atorvastatin 40 mg	24
Atorvastatin 80 mg	15

Table 3. Enrolled Patient Demographics (n = 71)

Characteristic	No. (%)
Age, y, mean ± SD	64.9 ± 10.5
Male	24 (33.8)
Female	47 (66.2)
Tobacco use	16 (22.5)
Hypertension	62 (87.3)
HDL <40 mg/dL	30 (42.3)
Documented family history	11 (15.5)
Diabetes, CAD, or equivalent	39 (54.9)

CAD indicates coronary artery disease; HDL, high-density lipoprotein.

Only 33.8% of statin changes were deemed appropriate (ie, an equipotent or greater potency agent was chosen as an alternate statin). For atorvastatin 10 mg, 59.1% of the conversions were considered appropriate; for atorvastatin 20 mg, 40% were considered appropriate; for atorvastatin 40 mg, 29.2% were considered appropriate; and for atorvastatin 80 mg, 0% were considered appropriate (Table 5). The mean time after January 1, 2007, until an alternate statin and dose were chosen was 2.9 months. During this time, patients were perceived to be without statin therapy because the pharmacy benefits manager did not allow for a grace period.

DISCUSSION

In this study, patients taking atorvastatin were changed to an alternate statin because of formulary restrictions. As a result, patients' total cholesterol, LDL, and triglyceride levels remained unchanged and HDL levels slightly increased, despite only 34% of conversions being considered therapeutically equivalent. Most data published regarding statin conversion evaluate changing to a uniform (usually more potent) statin, resulting in an improved lipid profile.[12-16] The data presented here suggest that the formulary change from a higher potency statin (atorvastatin) to a moderate potency statin (simvastatin, pravastatin, or lovastatin) does not affect the lipid profile as one may expect. Taken in conjunction with the 2004 update to the National Cholesterol Education Program Adult Treatment Panel III, these data should suggest to providers that moderate doses of generically available statins are just as effective as higher doses of brand-only statins for controlling lipid panels. Additionally, our data are unique in that they challenge previously published data that indicated usual care for formulary statin changes results in significantly worse LDL.[17]

High-density lipoprotein levels significantly increased for patients after switching statins (42.5 mg/dL to 44.4 mg/dL; $P = .018$). Clinically, this increase carries with it the potential for a decrease in myocardial infarction or death from coronary heart disease, as a 1-mg/dL increase in HDL has been linked to a 4.5% decrease in these outcomes.[18] This increase in HDL levels observed in the research results reported previously was expected. Previous research on the lipid-lowering potential of various statins suggests that as doses of atorvastatin approach 80 mg daily, the medication tends to decrease HDL rather than have a slightly positive or neutral effect.[11] The increase in HDL in this patient population does not translate into a decreased risk of myocardial infarction or death from coronary

Table 4. Mean Fasting Lipid Panel Results for Patients Changed From Atorvastatin to Another Statin

	Total Cholesterol (SD), mg/dL			HDL (SD), mg/dL		
Overall	Before	After	*P*	Before	After	*P*
n = 71, 10 mg	171.6 (39.9)	172.3 (36.8)	.885	42.5 (13.0)	44.4 (12.6)	.018
n = 22, 20 mg	165.9	166.0	.990	44.3	45.1	.480
n = 10, 40 mg	158.9	181.9	.019	40.0	43.8	.054
n = 24, 80 mg	175.0	169.5	.575	44.4	45.7	.361
N = 15	183.0	179.9	.816	38.4	41.6	.173

	LDL (SD), mg/dL			Triglycerides (SD), mg/dL		
Overall	Before	After	*P*	Before	After	*P*
n = 71, 10 mg	104.0 (50.9)	98.9 (29.5)	.417	145.8 (72.1)	142.5 (67.0)	.637
n = 22, 20 mg	94.7	92.4	.739	134.9	143.0	.549
n = 10, 40 mg	92.1	106.9	.082	133.9	155.9	.215
n = 24, 80 mg	102.7	97.4	.527	139.1	131.7	.545
N = 15	127.8	105.5	.373	180.5	150.1	.049

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein.

Table 5. Comparison of Lipid Panels Based on Appropriateness of Conversion

	Total Cholesterol, mg/dL		HDL, mg/dL		LDL, mg/dL		Triglycerides, mg/dL	
	Before	After	Before	After	Before	After	Before	After
10 mg appropriate n = 13 (59%)	174.3	170.1	42.1	43.7	101.3	94.0	155.1	162.7
10 mg inappropriate n = 9 (41%)	151.1	158.6	48.1	47.6	83.1	89.5	99.5	108.4
20 mg appropriate n = 4 (40%)	151.5	164.0	39.0	39.5	89.8	100.0	114.0	123.8
20 mg inappropriate n = 6 (60%)	163.8	193.8	40.7	46.7	93.7	111.5	147.2	177.3
40 mg appropriate n = 7 (29.2%)	146.1	153.6	41.0	42.7	80.3	86.1	124.9	123.6
40 mg inappropriate n = 17 (70.8%)	186.9	176.0	45.8	46.9	111.9	102.1	145.0	135.0
80 mg appropriate n = 0 (0%)	—	—	—	—	—	—	—	—
80 mg inappropriate n = 15 (100%)	183.0	179.9	38.4	41.6	127.8	105.5	180.5	150.1

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein.

heart disease, as this research was only designed to look at surrogate markers and did not assess clinical end points.

Low-density lipoprotein levels were expected to worsen, given the potential for suboptimal and delayed conversions. However, even with a 34% appropriate change rate, most aspects of the lipid panel remained unaffected. What was most concerning was the mean time to make the change from atorvastatin to an alternate statin (2.9 months). Although pharmacy records were not evaluated to determine whether the patient was treated during this time, we were cognizant that there was not a grace period for coverage and patients had little to no access to other sources for replacement prescriptions. Therefore, we were forced to work from the idea that patients went without medication. It is not known whether this lapse in therapy was harmful to patient outcomes, but some research shows that even brief discontinuation of statins may result in rapid elevations in surrogate markers related to myocardial infarction, including C-reactive protein and LDL.[23] Though this research shows that lipid profiles remained unchanged, the follow-up profiles were performed at least 6 weeks after initiating the alternate statin. Fasting lipid panel information was not available for the period of time between stopping atorvastatin and starting an alternate agent, so we cannot conclude how this delay affected this patient population's lipid profile during that time.

There are several challenges in interpreting these data, including patient adherence to statin therapy, the suggested slightly incremental improvements in lipid profiles when increasing statin strength or formulation, and the use of anticipated lipid-lowering effects as a marker for appropriate therapeutic interchange. These potential biases may explain how LDL concentrations in patients switched from atorvastatin 40 mg and 80 mg improved after providers changed agents.

First, the evidence surrounding patient adherence to statin therapy states that as many as 50% of patients will discontinue therapy within 6 months of the initial dose.[8,24] Given that we did not assess adherence to atorvastatin before its discontinuation, there is the possibility that patients were not taking their medication at the time of the lipid panel most immediately before changing therapies. The follow-up lipid panel often was performed within 6 months of changing therapy, so patients were more likely to be adherent to lipid-lowering therapy. Therefore, our postchange observation could show a lower LDL concentration, despite patients being on a less potent statin.

Second is the discussion about whether incremental increases or decreases in statin dose have significant lipid-reducing potential. On average, the LDL-lowering potential when incrementally increasing or decreasing a statin dose is approximately 6%.[11] This relatively small difference may not have been sufficient enough to show a significant change in lipid profiles, especially given the size of the population in this study. However, even with 66% of the dose changes

considered inferior conversions, the follow-up lipid profiles slightly trended toward improvement.

CONCLUSION

This research suggests that when this specific pharmacy benefit manager changed the formulary availability of a statin, control of a patient's lipid profile was not significantly affected. This research is based on individual effectiveness and not average patient outcomes. Patients switched from a high-potency statin to a moderate-potency statin, even though the majority of switches resulted in potency reductions, did not have worsening lipid panels.

The implications for managed care and third-party payers as a result of this study are favorable for decreasing medication costs without jeopardizing patient health. Formulary restrictions and the use of generic drugs can save $8 billion to $10 billion per year at retail pharmacies.[25] As the cost of prescription drugs continue to rise, generic substitutions that are identical or bioequivalent can prove useful to many third-party payers and managed care plans in providing a comprehensive prescription benefit without decreasing quality of patient outcomes.

Of greatest concern in this research is the almost 3-month delay in making the necessary medication regimen substitutions. Larger scale, controlled research that looks more closely at long-term morbidity and mortality outcomes within managed care plans or third-party payers with formulary restrictions will better identify any risks that may be associated with changing statin formulary availability. Until then, efforts should be focused on strategies to decrease the time it takes to make the necessary substitutions to formulary alternatives.

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