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Evidence of Sample Use among New Users of Statins: Implications for Pharmacoepidemiology

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Abstract

Background—Epidemiologic studies of prescription medications increasingly rely on large administrative healthcare databases. These data do not capture patients' use of medication samples. This could potentially bias studies of short-term effects where date of initiation may be inaccurate.

Objectives—Assess the extent of sample use among patients initiating statin therapy.

Research Design—Retrospective cohort of patients who filled a first prescription for a statin after at least 6 months of statin-free period in 2007-2010. LDL values obtained within the 15 days preceding the first prescription were analyzed using a 2-component Gaussian mixture model to look for evidence of prior treatment.

Subjects—A total of 26,033 statin initiators with at least 1 LDL lab within the 15 days preceding the prescription fill.

Measures—Estimators for the proportion of patients filling a new prescription already on treatment.

Results—Among 9,256 patients filling a branded statin, LDL distribution was bimodal, consisting of 2 Gaussian distributions: one, which made up 13.4% of the total population, had much lower LDL values (mean=71.8 mg/dL) compared to the second (mean=148.0 mg/dL), suggesting drug use prior to first dispensed prescription. Among 16,777 patients filling a generic statin, LDL levels were substantially higher with no evidence of bimodality that would suggest prior sample use.

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Conclusion—These results provide indirect evidence that the initial period of branded medication use may often be missed when using pharmacy claims data to define drug initiation. Further research is needed to examine approaches to better identify incident medication use when assessing short-term effects.

Keywords

claims databases; epidemiologic methods; exposure misclassification; sample drugs

INTRODUCTION

Large healthcare claims databases are widely used in pharmaceutical outcome research, drug safety surveillance, and healthcare quality improvement programs.[1-5] These databases capture information on dispensed medications through claims sent by the pharmacy to the pharmacy benefit manager. Because this information on medication exposure is collected prospectively, it is not prone to recall or interview bias. However, concerns have been raised about the data incompleteness.[6, 7] A recent US study of patients being anticoagulated for atrial fibrillation found that approximately 10% of patients receiving regular monitoring to manage medications had no evidence of medication use in the pharmacy claims.[8]

Incomplete capture of prescription medications may result when patients use drugs during hospital stay, [6] use a spouse's pharmacy benefit, or pay cash for prescriptions.[7] No record of these drugs will exist in the insurance pharmacy claims data. Another contributing factor to misclassified drug exposure results from the use of free samples. In 2010, the pharmaceutical industry provided medication samples worth $14 billion to physicians.[9] A survey conducted in 2006 found that 58% of physicians frequently give samples to patients.[10] Free samples are given to find the optimal dose or test for efficacy and tolerability of medication before a patient starts on a long-term treatment.[11-13]

Missing information on prescription medication use may adversely affect research and quality improvement activities that rely on these data.[14-17] To understand the potential impact of missing data due to sampling on these activities, we sought to estimate the prevalence of free sample use among statin initiators in a large healthcare database. We used a new design that considers low-density lipoprotein (LDL) test results before the first prescription claim to assess the probability that patients filling a prescription may already be on treatment. Since guidelines recommend monitoring statin therapy by checking LDL levels shortly after the start of treatment,[18] we assumed that many physicians would provide a first course of treatment using samples and would monitor these laboratory values before writing a long-term prescription. We used the distribution of LDL just before the first dispensed prescription to estimate the proportion of patients receiving a first course of treatment via samples.

METHODS

Data sources and study population

We identified a cohort of patients initiating statin treatment using the Truven Health Analytics MarketScan® Commercial Insurance Claims and Encounters and Laboratory Results Databases for the years 2007-2010. These databases represent the medical experience of insured employees and dependents in the US with primary coverage through privately insured fee-for-service, point-of-service, or capitated health plans. All enrollment records and inpatient, outpatient, ancillary, and pharmaceutical drug claims are collected for approximately 20 million people annually from over 100 nationwide insurers. Laboratory results are available on patients who have the test ordered and the sample sent to a specific national testing company. Personal identifiers are removed from all analytical data files. The UNC Institutional Review Board approved this study.

Using these data and a new-user design, we identified a retrospective cohort of patients who were statin new users between July 1st, 2007 and July 1st, 2010. New users of statins were defined as patients who had a prescription claim for any statin formulation following 6 statin-free months of observed plan enrollment, and the index date was the first statin prescription fill date. To ensure patients were utilizing pharmacy benefits, at least 1 prescription claim was required on any non-statin medication during the 6-month period preceding the index date. The cohort consisted of new users at least 40 years old at the index date who had at least 1 LDL lab result between 0 and 300 milligrams per deciliter (mg/dL) during the 6 statin-free months. Patients who had their last LDL lab obtained more than 15 days prior to the index date were excluded. The study design and cohort creation process are illustrated in Figure 1 and Figure 2.

We created a number of covariates for demographic information, clinical conditions and co-medications based on claims occurring in the 6-month period preceding the index date. Conditions were derived using definitions consisting of diagnoses with relevant International Classification of Diseases, Ninth Revision, Clinical Modification codes, procedures with Current Procedural Terminology codes, and medication usage with National Drug Codes, merged with REDBOOK supplement. The values of LDL labs were identified by the Logical Observation Identifiers Names and Codes (LOINC®) in the Laboratory Results Database (LOINC: 13457-7).

Statins and LDL

Statins, the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, are used to lower LDL levels to prevent cardiovascular disease events.[19, 20] While the 2013 guidelines move away from a specific LDL value, [21] according to guidelines in effect during the study period, statin treatment decisions were largely determined by LDL level, with less than 100 mg/dL deemed optimal, and lipid panels were closely monitored before and during treatment.[18, 22] Statins are highly effective at lowering LDL levels with 90% of therapeutic response apparent within 2 weeks.[23] Systematic reviews of several placebo-controlled trials showed that LDL reduction from baseline ranged from 18% to 58% among participants receiving statins.[18, 24-25] A randomized, parallel-group, comparator-controlled trial also

showed a reduction of 20-55% by the end of 6 weeks.[26] Branded statins are one of the most frequently reported free drug samples,[27] and samples are generally used to provide a first course of therapy. We classified index statin drugs as branded or generic based on the drug's patent status at the time of prescription fill.

Statistical analyses

Because statins are highly effective at lowering LDL levels, patients on treatment will have a different distribution of LDL compared to those not on treatment. If patients filling a first prescription for a statin are a mix of patients already being treated (through the use of samples) and newly treated patients, the distribution of LDL prior to first fill will follow a mixture distribution.[28]

Based on the observation of the LDL distributions in Figure 3 and Figure 4 and its biological plausibility, we modeled the distribution of LDL prior to first fill, LDL_1 using a 2-component Gaussian mixture model.[29] Given only observations on the pooled population with no sub-population identity information, finite mixture models are a useful way to model unobserved heterogeneity and make statistical inferences about the properties of the sub-populations. The areas of application of finite mixture models, also known as latent class models and unsupervised learning models range from epidemiology,[30] genetics,[31] medicine[32] to economics[33] and marketing.[34] The 2-component Gaussian mixture model provided an estimate for the parameters of the 2 distributions via maximum likelihood estimation using EM algorithms. The 2 distributions are reported as D (mean μ, standard deviation σ), where D_1 refers to the distribution with the lower mean and D_2 corresponds to the distribution with the higher mean. The mixing proportion parameter λ from the mixture model provides an estimate of the percentage of patients already on treatment. The difference in means between the 2 distributions provides an estimate of the treatment effect, which is already approximately known from trials, and permits an assessment of the model's plausibility. Since free samples of branded statins are frequently distributed[27] while samples of generic statins are rarely offered,[35] analyses were performed in branded and generic statin users separately. Descriptive statistics were calculated and assessed for clinical and demographic covariates.

To further confirm that there were prevalent users mixed in the identified new user cohort, we compared the distributions of LDL_1 to LDL_2, an older LDL performed before LDL_1, in patients with at least 2 sequential LDL labs in the 6 statin-free months preceding the index date. In these patients, we expected that the first LDL, LDL_2 would motivate the start of treatment (that may have been initiated through samples), and the second LDL, LDL_1 would be ordered to check the effectiveness of the first course of treatment on LDL levels. The older LDL_2 could then serve as a negative control, an indicator for the absence of confounding. Finite mixture model analyses described above were performed in branded and generic statin users separately.

To assess the robustness of the results and the possibility that a mixture distribution of LDL was caused by other reasons, sensitivity analyses were conducted by restricting the analyses to cohorts of patients without prevalent non-statin lipid-lowering medications, recent

hospitalization or emergency room visits, or specific indications for statins including history of diabetes, stroke, stenting or stress test, separately.

Descriptive statistics were calculated using SAS version 9.2 (SAS Institute, Cary, North Carolina). All mixture model analyses were performed using R statistical software.

RESULTS

Between July 1st, 2007 and July 1st, 2010, we identified 26,033 continuously-enrolled patients with pharmacy insurance benefits having a prescription fill for statins after a 6-month statin-free period and at least an LDL laboratory value between 0 and 300 mg/dL with the lab done within 15 days prior to the index date. Among them (Table 1), 35.6% initiated on a branded statin, and 54.2% were female. The age at fill date ranged from 40 to 96 years old and averaged around 53 years in both user groups. The distribution of clinical conditions including coronary syndromes, kidney diseases, and some metabolic syndromes were similar in both user groups of generic and branded statins. People who had a stress test, hyperlipidemia diagnoses or use of non-statin lipid-lowering co-medications within the last 6 months were more likely to initiate a branded statin.

The distribution of LDL_1, the last LDL just before the first dispensed statin prescription, is presented in Figure 3. The distributions are reported as D (mean μ, standard deviation σ), where D stands for distribution. Among all 26,033 patients with at least 1 LDL result available, the LDL level in the branded drug users had a bimodal distribution, corresponding to a mixture of 2 normal distributions, D_1 (71.8 mg/dL, 20.7 mg/dL) and D_2 (148.0 mg/dL, 36.8 mg/dL). The percentage of patients who had free statin samples was estimated to be 13.4% in those filling a branded drug prescription. In comparison, the LDL level in the generic drug users was estimated to be from a more homogeneous population.

To further examine if the date of drug initiation was misclassified in some patients having utilized free drug samples, we compared the distributions of 2 sequential LDL labs in both branded and generic drug user groups and presented the results in Figure 4. In this more restrictive cohort, 5,698 patients had at least 2 LDL lab results available before filling a statin prescription. The median time between the 2 LDL labs was 99 days. Similarly to patients with at least 1 LDL lab result, the distribution of LDL_1 in branded drug user group was estimated to be a mixture of 2 normal distributions: D_1 (75.4 mg/dL, 18.6 mg/dL) and D_2 (136.8 mg/dL, 37.0 mg/dL) while that of LDL_1 in generic users was more homogeneous. As expected, the distribution of LDL_2, the older LDL lab performed before LDL_1 were shown to be from homogeneous distributions for both branded and generic drug users. Among these patients initiating a branded drug, 25.6% of them were estimated to have had free drug sample exposure.

Similar results were observed when we conducted sensitivity analyses in patients with no recent hospitalization or emergency room visits, no specific indications for statins distinct from elevated LDL levels, or no use of non-statin lipid-lowering medications separately. In all cohorts, the LDL distributions were more homogenous in generic statin users, while there

was evident bimodality in the LDL distributions in branded statin users with estimates consistent with those of primary analyses.

DISCUSSION

In this study of patients starting statin lipid-lowering treatment, we found strong evidence of prior medication use among patients filling a first prescription. Among patients filling a first prescription for a branded statin, we observed a bimodal distribution of LDL lab values recorded just before the first prescription fill, with many LDL levels well below treatment targets for statin therapy. Using a 2-component Gaussian mixture model, we estimated that about 1 in 7 of those patients filling a first prescription for a branded statin had evidence of first course of treatment using samples prior to first prescription claim. Among patients filling a prescription for a generic statin, the LDL distribution had no evidence of bimodality that would suggest prior treatment. We think that sample use is the most likely explanation for these findings, since samples would be associated with the use of branded medications, but not generic.

There are other potential reasons why earlier treatments may not be captured in the pharmacy claims. For example, treatment will not be captured if patients use supplements or over-the-counter medications, pay cash for prescriptions, use a spouse's pharmacy benefit, [7] or use drugs during hospital stay.[6] However, the likelihood of these occurrences should be similar, if not higher among users of generic compared to branded medications. Sensitivity analyses with patients who had no recent hospital stay or emergency room visit also showed no change in the results.

Besides treatment through samples, we considered other possible explanations for the bimodal distribution of LDL before the first prescription fill of a branded statin. For example, therapeutic lifestyle changes (TLC) through dietary therapy, weight management and exercise are normally initiated before or along drug therapy and could also contribute to the decrease in LDL level with a mean reduction of 11%.[18] Due to its essential role in cholesterol management and common practice as the initial step, however, the effect of TLC on LDL level should be similar in both users of generic and branded medications. The bimodal distribution could also be a result of different populations of patients having different LDL targets depending on their risk profiles for cardiovascular diseases.[19] However, when these patients with specific indications distinct from elevated LDL including history of diabetes, stroke, stenting or stress test were excluded, results similar to the original cohort were observed with differential presence of bimodality in the branded medication users, suggesting sample use was the most plausible explanation.

Patients initiating statin therapy for lipid management are recommended to have LDL levels evaluated every 6 to 8 weeks until the goal level is achieved.[18] In patients with 2 labs available prior to the first prescription fill, we expected that the first LDL would motivate the start of treatment (that may have been initiated through samples), and the second LDL would be ordered to check the effectiveness of the first course of treatment on LDL levels. Our analysis supports this hypothesis. Among patients who had at least 2 sequential LDL labs values during the baseline period, the last recorded LDL exhibited strong evidence of

bimodality among branded medication users; whereas the first LDL observed exhibited no evidence of bimodality and had a higher mean that was consistent with LDLs from an untreated hyperlipidemic population.[25] This analysis suggested that pre-treatment pattern of testing can be used to identify patients starting treatment on samples.

These findings in our study provided evidence that the date of drug initiation can be misclassified in some patients due to free sample drug utilization when using pharmacy claims data to ascertain exposure status. The result was most pronounced in people filling a branded statin. It is possible for patients filling a prescription for a generic drug to receive samples but the likelihood is low.[11] It is possible, however, that some patients initiated on a branded drug sample decided to switch to a generic drug. Perhaps because the effect of the drug was not satisfactory, the patients were intolerant to side effects, or they preferred to reduce the co-pay. If this happens at all, it seems to be rare, however, and we were not able to detect the mixture in our analysis. Because of the requirement of having at least 1 statin prescription fill, our analysis did not include patients who initiated treatment via consecutive free samples and never received a prescription for a statin. The presence of these patients could affect studies including non-users.

Our study has important implication for pharmacoepidemiologic research and quality of care research using US healthcare claims databases. In particular, events that occur while a patient is taking samples may not be appropriately linked to the medication. Since samples are often used at the start of treatment,[11-14] early events caused by the medication could be missed. This could cause medications that are provided as samples to appear safer with respect to the short-term risk of adverse events. This will need to be taken into consideration by the various drug safety surveillance activities that rely on these data. In studies where a drug that is often provided as samples is being compared to a drug that is not, the drug provided via samples through early events would be missed. The magnitude of bias caused by this exposure misclassification will depend on the extent of free sample use and the incidence of early adverse events in the exposure groups.[14, 36]

Misclassification of exposure may be particularly problematic for case-only designs, including self-controlled case series, case-crossover and sequence symmetry analyses, since these designs are more susceptible to bias due to exposure measurement error than conventional studies.[37] In studies that compare branded to generic medications, the apparent new users of branded medications may consist of many patients who have already been receiving treatment through the use of samples. These are patients who are more likely to be tolerant of treatment, to perceive a benefit of treatment, and also more likely to be adherent to therapy.[38, 39] This could lead to systematic differences between the exposure groups. When patients start treatment on samples, cumulative exposure will also be under-ascertained among new users of branded medications. This could lead to slightly exaggerated estimates of both the benefits and risks associated with short-term exposures but it is likely to be small for longer-term exposures. For pharmacoepidemiologic research that attempts to control confounding by using laboratory values, care must be taken to make sure that the laboratory values are assessed prior to the true start of treatment. Controlling for post-treatment variables can increase rather than decrease bias in point estimates to the extent that they serve as causal intermediates.[40]

We have identified a potential issue for exposure misclassification due to missing information on sample use when conducting research using pharmacy claims data, but we do not yet have solutions to address it. This is a complex issue and deserves additional research to examine approaches that can be used to better identify true incident medication use. Our research suggests that looking at timing of tests and physician visits prior to medication initiation may be useful for identifying patients who have likely been receiving samples. For example, for drug therapy such as statin therapy that requires follow-up testing, it appears that restricting the analysis to patients who have a single LDL immediately prior to treatment may substantially reduce the percentage of patients starting treatment on samples. For medications that do not require immediate follow-up with a physician for dose titration, simply requiring a physician visit shortly prior to the first pharmacy claim may exclude patients who start treatment using samples. Another possible approach is to start follow up after a fix period of time following the second prescription fill for all comparison groups. This approach, however, may not be optimal in situations where very early events are of interest, due to the depletion of susceptibles.

Our study has several important limitations. First, our analysis focused only on patients with private insurance in the US and therefore may not generalize to other populations, such as those with Medicaid or Medicare. Second, our results will not necessarily generalize to other medications, other study periods or research databases in other countries. Due to different patent status, promotional expenditures, pharmaceutical policies and regulations, the amount of missing data due to free drug sample utilization will change. It may be important for researchers to take into account the prevalence of sample use in the time period in which a study is done. Moreover, LDL laboratory results were only available if the blood sample was sent to a specific national testing company. If samples were tested in the clinic or sent to a different testing company, the LDL results would be missing. However, the average values of LDL measurements in these data were close to their population means, as estimated from a nationally-representative data from the National Health and Nutrition Examination Survey.[41] Therefore, we think missing LDL results are not likely to have an important effect on generalizability.

In conclusion, we found evidence that a substantial portion of patients filling branded prescriptions for statin medications were likely to have received drug samples previously and that in these patients the start date of therapy based on pharmacy-dispensing data would be incorrect. This finding has important implication for pharmacoepidemiology and quality of care research using US healthcare databases. Caution must be exercised when ascertaining start date for drug exposure using pharmacy-dispensing data from healthcare claims databases, especially for short-term effects when branded medications that are available as samples are compared to generic medications. Further research is needed to identify study designs that minimize exposure misclassification in comparative new-user studies of medications that many patients may start through the use of free samples.

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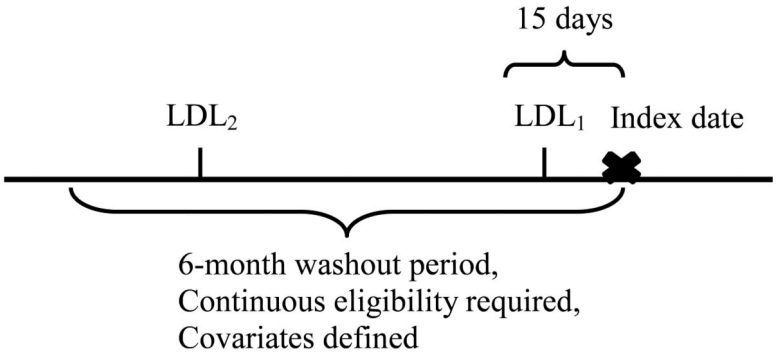

Figure 1.
Schematic of the statin user cohort study design. Not all patients had LDL_2 in the primary cohort.

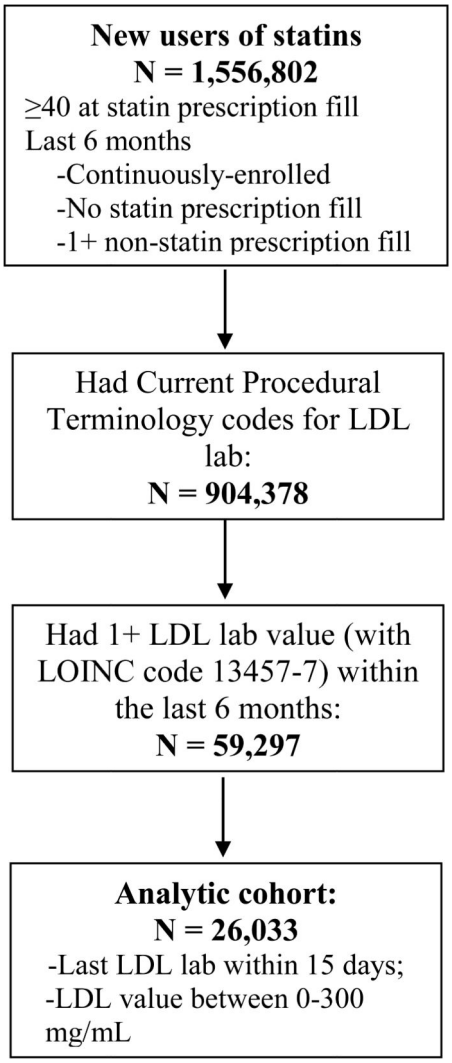

Figure 2.

Flow diagram of the cohort creation process: new users of statins, ≥40 years of age, United States, 2007-2010

(a)

Parameters	Branded (N=9,256)		Generic (N=16,777)	
	D_1	D_2	D_1	D_2
λ	0.134	0.866	0.488	0.512
μ (mg/dL)	71.8	148.0	139.1	148.8
σ (mg/dL)	20.7	36.8	42.1	23.3

(b)

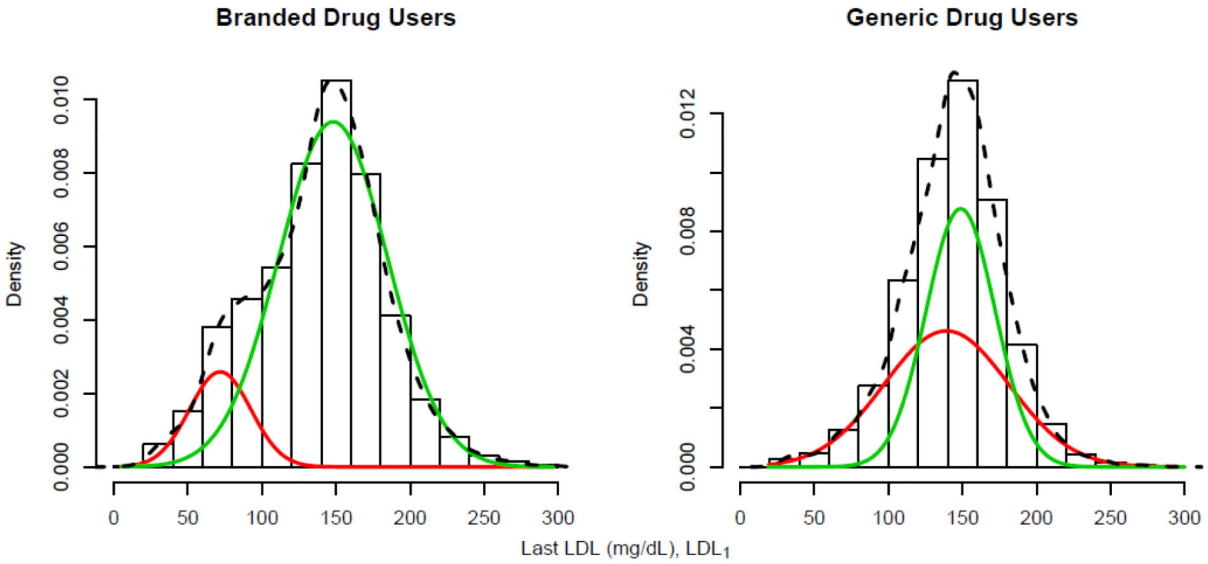

Figure 3.

The distribution of last LDL before first statin prescription fill in patients with at least 1 LDL lab prior to first statin prescription fill.

((a) Results from mixture model analysis: λ =proportion, μ =mean (mg/dL), σ =standard deviation (mg/dL), *D* =distribution;

(b) Left panel: Patients filling a prescription for branded drug; Right panel: patients filling a prescription for generic drug)

(a)

	Parameters	Branded (N=2,392)		Generic (N=3,306)	
		D_1	D_2	D_1	D_2
LDL_1	λ	0.256	0.744	0.710	0.290
	μ (mg/dL)	75.4	136.8	133.7	143.9
	σ (mg/dL)	18.6	37.0	38.3	20.7
LDL_2	λ	0.881	0.119	0.536	0.464
	μ (mg/dL)	130.8	145.1	129.5	136.6
	σ (mg/dL)	42.9	16.7	41.8	23.7

(b)

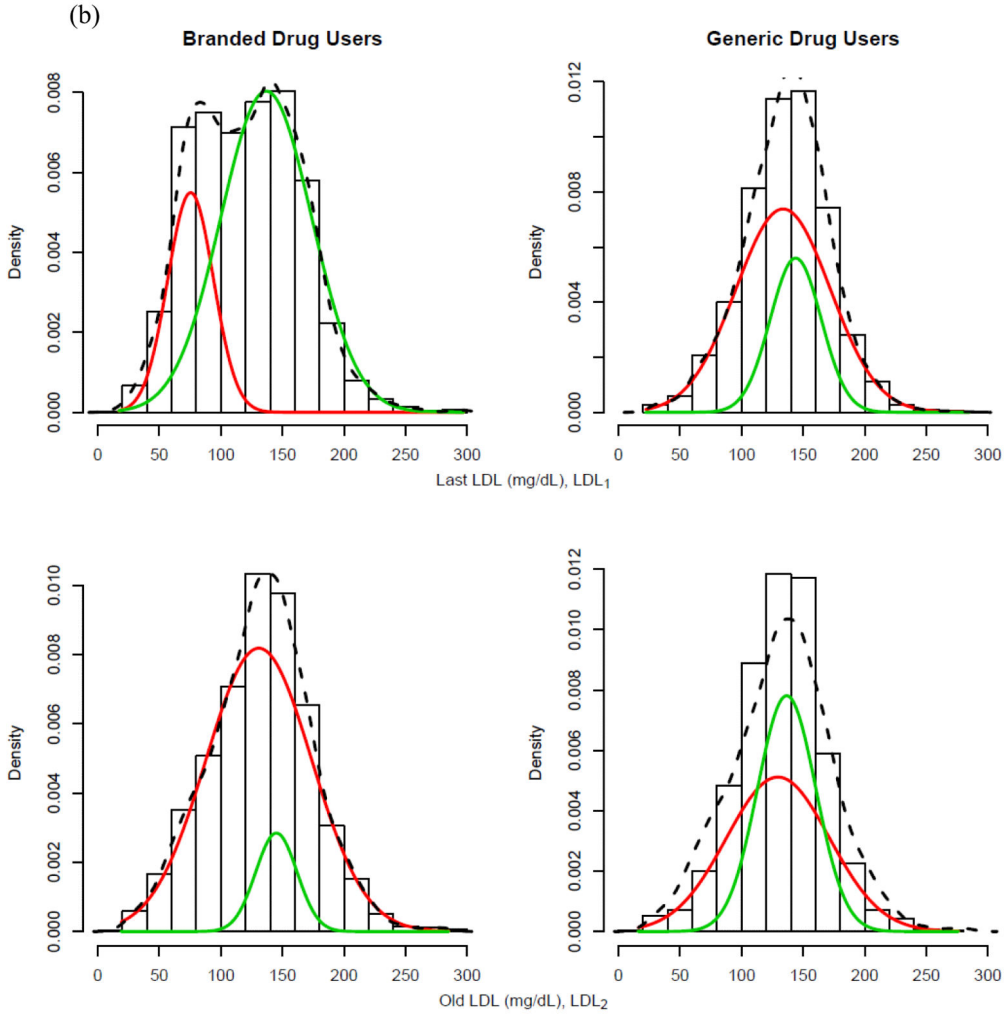

Figure 4.

The distributions of 2 sequential LDLs before first statin prescription fill in patients with 2 or more LDL labs prior to first statin prescription fill.

((a) Results from mixture model analysis: λ =proportion, μ =mean (mg/dL), σ =standard deviation (mg/dL), *D* =distribution;

(b) (Top panels: the last LDL, LDL_1; Bottom panels: the older LDL, LDL_2; Left panels: Patients filling a prescription for branded drug; Right panels: patients filling a prescription for generic drug)

Table 1

Demographic and Clinical Characteristics of the New Users of Statins Who Initiated Between July 1, 2007 and July 1, 2010, ≥40 Years of Age, United States

	Percentage, %		
	Generic[a] N=16,777	**Branded[b] N=9,256**	**All N=26,033**
%	64.4	35.6	100.0
Age, Mean (SD), year	53.9 (7.9)	52.7 (6.7)	53.4 (7.5)
Gender			
Female	55.3	52.3	54.2
Comorbidities			
Chronic Heart Failure	1.0	1.0	1.0
Stroke	2.7	2.6	2.7
Hyperlipidemia	61.3	70.9	64.7
Hypertension	44.1	45.9	44.7
Type 2 Diabetes	25.1	23.3	24.4
Coronary Syndrome			
Atrial Fibrillation	1.4	1.4	1.4
Unstable Angina prior to the last 3 weeks	0.3	0.5	0.4
Unstable Angina in the last 3 weeks	0.4	0.5	0.4
Myocardial Infarction in the last 3 weeks	0.4	0.2	0.3
Kidney Disease			
Acute Kidney Injury	0.2	0.2	0.2
Chronic Kidney Diseases	1.5	1.7	1.6
Dialysis	0.0	0.0	0.0
End Stage Renal Disease	0.1	0.1	0.1
Procedures			
Stenting	0.5	0.7	0.6
Stress Test	4.6	7.4	5.6
Emergency room visit in last 2 weeks	2.9	2.1	2.7
Hospitalization in last 2 weeks	1.4	0.7	1.1
Co-medications			
Ezetimibe	1.5	2.6	1.9
Fibrates	4.4	5.3	4.7
Nicotinic acid	0.7	1.6	1.0

Note: The percentages presented are column percentages. SD = standard deviation

[a] During the study period, the generic drugs initiated were Lovastatin, Pravastatin Sodium and Simvastatin.

[b] During the study period, the branded drugs initiated were Advicor (Lovastatin/Niacin), Caduet (Amlodipine Besylate/Atorvastatin Calcium), Crestor (Rosuvastatin Calcium), Lipitor (Atorvastatin Calcium), Lescol (Fluvastatin Sodium), Simcor (Simvastatin/Niacin) and Vytorin (Ezetimibe/Simvastatin).