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Original Paper

Reasons for Discontinuation of Lipid-Lowering Medications in Patients with Chronic Kidney Disease

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Key Words
Medication discontinuation · Chronic kidney disease · Lipid-lowering medications

Abstract
Background/Aims: Many patients with chronic kidney disease (CKD) do not receive lipid-lowering therapy despite their high cardiovascular risk. The reasons for this are unknown. ***Methods:*** We have conducted a retrospective cohort study of discontinuation of lipid-lowering drugs in patients with CKD stage 3 and higher treated in practices affiliated with two academic medical centers between 2000 and 2010. Information on medication discontinuation and its reasons was obtained from electronic medical records, including natural language processing of electronic notes using previously validated software. ***Results:*** Out of 14,034 patients in the study cohort, 10,072 (71.8%) stopped their lipid-lowering drugs at least once, and 2,444 (17.4%) stopped them for at least 1 month. Patients who had a comorbidity associated with higher cardiovascular risk were less likely to stop lipid-lowering drugs. Insurance request was the most common explicitly documented reason for discontinuation, and adverse reactions were the most common reason for long-term discontinuation. In a multivariable analysis, patients were more likely to stop a lipid-lowering drug because of an insurance request if they had government insurance and they were also more likely to stop a lipid-lowering drug because of adverse reactions if they had a history of multiple adverse reactions to other medications. There was no significant relationship between CKD stage and the reason for discontinuation of lipid-lowering drugs. ***Conclusions:*** Patients with CKD frequently stop lipid-lowering drugs. Insurance requests and adverse reactions are common reasons for the discontinuation. Further research is needed to ensure appropriate lipid-lowering therapy for these individuals at high cardiovascular risk.

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Introduction

The prevalence of chronic kidney disease (CKD) is increasing. In the US, the number of patients enrolled in the end-stage renal disease Medicare-funded program increased from approximately 10,000 in 1973 to over half a million in 2008 [1], and the overall prevalence of CKD is 11% [2]. Kidney failure is associated with high morbidity and mortality; it is the 9th most common cause of death in the US. Patients with CKD are at a particularly high risk for cardiovascular events [3, 4]. Recent studies show that lipid-lowering agents decrease the rate of cardiovascular events in this population [5–7], and the latest guidelines recommend that most adult patients with nondialysis-dependent CKD should be treated with a lipid-lowering regimen [8].

Despite the evidence of its benefits, lipid-lowering therapy remains underutilized in patients with CKD [9–11]. The reasons for this are not well understood. One possible contributor is discontinuation of lipid-lowering medications by patients and/or their providers – a common phenomenon in the general population [12–16]. Discontinuation of lipid-lowering medications can lead to an increase in cardiovascular risk [17, 18]. However, the reasons for discontinuation of lipid-lowering medications are not well studied. Neither the prevalence nor the reasons for discontinuation of lipid-lowering medications have been investigated in patients with CKD.

In the past, most analyses of outpatient medication treatment were confined to administrative/claims data. These data sources can identify patients who stopped taking their medication, but they contain little information about the reason for discontinuation. With the advent of electronic medical records (EMR), it has become possible for clinicians to record the reason why they discontinue a medication. We therefore conducted a large retrospective study of EMR data to analyze the frequency and reasons for discontinuation of lipid-lowering medications in patients with moderate to severe CKD.

Subjects and Methods

Design

We conducted a retrospective cohort study to evaluate reasons for discontinuing lipid-lowering medications and to determine factors associated with these reasons.

Study Cohort

Study participants included adult patients with CKD stage 3 and higher who were followed by primary care physicians associated with Brigham and Women's Hospital or Massachusetts General Hospital, Boston, Mass., USA, for at least 1 year and who had at least one lipid-lowering medication prescribed during the study period from January 1, 2000, to December 31, 2010. Patients were excluded from the study if demographic information (age, gender, or zip code) was unavailable.

This study was approved by the Institutional Review Board at Partners HealthCare System, and the requirement for written informed consent was waived.

Study Measurements

An individual patient served as the unit of analysis. The following classes of lipid-lowering medications were included in the analysis: statins, fibrates, niacin, cholesterol absorption inhibitors, and bile acid sequestrants. Lipid-lowering medication discontinuations were identified from explicit discontinuation records in the EMR or inferred from the absence of a refill prescription for 12 months. The absence of a refill prescription was only interpreted as medication discontinuation if the patient continued to be seen in the practice as evidenced by EMR notes. If a patient had multiple discontinuations of lipid-lowering medications, only the first discontinuation was included in the analysis to avoid clustering within individual patients. A patient was considered to have replaced a discontinued lipid-lowering agent with another one if the new medication was prescribed within 30 days of the discontinuation; otherwise it was counted as a long-term discontinuation. Information on the reasons for discontinuation was obtained from a combination of structured EMR data and

computational processing of encounter notes. Clinicians are required to select a reason for discontinuation in the EMR when the medication is explicitly discontinued. Reasons were categorized as one of the following: (a) adverse reaction, (b) too expensive, (c) change requested by insurance, (d) ineffective, or (e) other. The 'other' category included the 'no longer necessary' option representing the default selection of the EMR discontinuation reason dialog box, free text entries as well as medications whose discontinuation was inferred from the 12-month absence of prescriptions (which therefore did not have an explicit discontinuation reason documented). Medications discontinued because of an adverse reaction were also identified through natural language processing analysis of provider notes in the EMR. The TextMiner software used to detect adverse reactions has been previously shown to have a sensitivity of 86.5% and a specificity of at least 91.9% [19].

Patient age was calculated at the study entry. CKD stage was determined using two estimated glomerular filtration rate (eGFR) measurements at least 3 months apart that were calculated using the Modified Diet in Renal Disease (MDRD) formula [20]. If a combination drug was discontinued and a noncombination lipid-lowering medication was started within 30 days, the assignment of the class of the discontinued medication was made based on the completely discontinued component of the combination medication. Diagnoses of coronary artery disease, diabetes mellitus, peripheral vascular disease, and hypertension were established from the EMR data.

Demographic information, medication, and laboratory data were obtained from the EMR at Partners HealthCare System, an integrated healthcare system in Eastern Massachusetts which includes Brigham and Women's Hospital and Massachusetts General Hospital. The Partners HealthCare EMR system was fully integrated by 2000, so it includes all prescription and laboratory records for patients over the study period. No changes have been made to this system over the 10 years of this study.

Statistical Analysis

Summary statistics were calculated using frequencies and proportions for categorical data and means (SDs), medians, and ranges for continuous variables. Quantitative variables were compared across multiple patient categories using one-way ANOVA and categorical variables using χ^2 test. A multinomial logistic regression model was used to identify patient characteristics associated with specific reasons for discontinuation, compared to no discontinuation. Patient demographics [age, sex, race, health insurance type (private, government, or none), and median income by zip code], comorbid conditions (coronary artery disease, diabetes mellitus, peripheral vascular disease, a history of a cerebrovascular accident and hypertension), CKD stage, class of lipid-lowering medication (statin, nonstatin, or combo), a history of multiple adverse reactions to nonlipid-lowering medications and whether the drug was discontinued before or after the introduction of generic simvastatin on January 1, 2007, were included as covariates in the analysis. Thresholds for statistical significance were adjusted for multiple hypothesis testing using the Simes-Hochberg method [21, 22]. All data was analyzed using SAS version 9.3 (SAS Institute, Cary, N.C., USA).

Results

Study Cohort

We identified 14,505 patients with CKD stage 3 and higher who were followed by Brigham and Women's Hospital or Massachusetts General Hospital primary care physicians and were taking at least 1 lipid-lowering medication between 2000 and 2010. We excluded 471 patients who had missing demographics information. The remaining 14,034 patients were included in the analysis (table 1).

The study patients had a median age of 69 years; nearly 60% of the patients were women. Most (90%) patients had CKD stage 3A or 3B. Nearly 75% of the patients had other comorbidities associated with an increase in cardiovascular risk, including coronary artery disease, cerebrovascular disease, peripheral vascular disease, diabetes mellitus, or hypertension. Over 87% of the patients were taking statins (alone or in combination with other lipid-lowering agents).

Lipid-Lowering Medication Discontinuation

More than 70% of the patients discontinued their lipid-lowering medication at least once after a median of 2.2 years on the drug. Nearly 1 in 5 patients discontinued the medication for at least 1 month. Patients who never discontinued their lipid-lowering medication were more

Table 1. Patient characteristics

Variable	Never stopped	Replaced with another drug	Stopped long-term	p value
Patients	3,962	7,628	2,444	
Age, years	72.5±11.8	66.8±11.5	67.7±12.4	<0.0001
Women	2,364 (59.7)	4,486 (58.8)	1,509 (61.7)	<0.0001
Race/Ethnicity				<0.0001
White	3,393 (85.6)	6,114 (80.2)	2,022 (82.7)	
Black	171 (4.3)	470 (6.2)	152 (6.2)	
Hispanic	187 (4.7)	491 (6.4)	124 (5.1)	
Asian	70 (1.8)	186 (2.4)	52 (2.1)	
Other[1]	141 (3.6)	367 (4.8)	94 (3.9)	
Health insurance				<0.0001
Private	1,183 (29.9)	1,890 (24.8)	614 (25.1)	
Public	2,752 (69.5)	5,674 (74.4)	1,810 (74.1)	
Other[2]	27 (0.7)	64 (0.8)	20 (0.8)	
Median income by zip code, USD 1,000	57.3±21.5	57.2±22.3	59.0±23.2	0.0015
CKD stage				<0.0001
3A	2,653 (67.0)	5,160 (67.7)	1,547 (63.3)	
3B	919 (23.2)	1,744 (22.9)	605 (24.8)	
4	315 (8.0)	558 (7.3)	208 (8.5)	
5	75 (1.9)	166 (2.2)	84 (3.4)	
Coronary artery disease	1,123 (28.3)	1,755 (23.0)	522 (21.4)	<0.0001
Diabetes mellitus	404 (10.2)	1,293 (15.6)	268 (11.0)	<0.0001
Hypertension	2,712 (68.5)	4,732 (62.0)	1,487 (60.1)	<0.0001
Cerebrovascular accident	393 (9.9)	447 (5.9)	156 (6.4)	<0.0001
Peripheral vascular disease	233 (5.9)	384 (5.0)	109 (4.5)	0.032
History of multiple adverse reactions to medications	1,043 (26.3)	2,446 (32.1)	911 (37.3)	<0.0001
Lipid-lowering medication started before 2007	264 (6.7)	1,946 (25.5)	494 (20.2)	<0.0001
Lipid-lowering medication class				<0.0001
Statin	3,548 (89.6)	6,563 (86.0)	1,700 (69.6)	
Nonstatin	181 (4.6)	905 (11.9)	677 (27.7)	
Combination drug[3]	233 (5.9)	160 (2.1)	67 (2.7)	
Low-density lipoprotein value, mg/dl	89.6±32.1	97.2±38.3	104.9±42.5	<0.0001
eGFR, ml/min/1.73 m^2	47.7±13.1	49.4±15.1	48.2±16.3	<0.0001

Values are given as numbers (%) or means ± SD.

[1] Includes unknown.

[2] Includes none.

[3] A combination of a statin with another lipid-lowering medication.

likely to be white, have private health insurance, and have a comorbidity associated with an increase in cardiovascular risk (table 1). Patients who discontinued lipid-lowering medications for a long time were more likely to be female, to have a history of multiple adverse reactions to medications, and to be taking a nonstatin medication, while patients who replaced one lipid-lowering medication with another were most likely to have started lipid-lowering treatment before 2007, when generic simvastatin was introduced.

Reasons for Lipid-Lowering Medication Discontinuation

Overall, apart from the default selection 'no longer necessary', change requested by the insurance was the most common explicitly declared reason for discontinuation of lipid-

Table 2. Reasons for discontinuation of lipid-lowering medications

	Before 2007	After 2007
No new drug started, n (%)		
Adverse reaction	211 (10.82)	104 (21.05)
Change requested by insurance	29 (1.49)	8 (1.62)
Ineffective	22 (1.13)	4 (0.81)
Other	1,671 (85.69)	375 (75.91)
Too expensive	17 (0.87)	3 (0.61)
Subtotal	1,950 (19.36)[1]	494 (4.90)[1]
New drug started, n (%)		
Adverse reaction	270 (4.75)	180 (9.25)
Change requested by insurance	977 (17.19)	403 (20.71)
Ineffective	164 (2.89)	84 (4.32)
Other	3,871 (68.13)	1,195 (61.41)
Too expensive	400 (7.04)	84 (4.32)
Subtotal	5,682 (56.41)[1]	1,946 (19.32)[1]

[1] Percent of all 10,072 patients who discontinued lipid-lowering medications.

lowering medications, recorded for 1,417 patients (14% of all patients who ever discontinued a lipid-lowering medication). Adverse reaction (765 patients, 7.6%) was the second most common reason. As expected, change requested by the insurance was far more common among patients whose lipid-lowering medication was replaced with another agent (table 2). Adverse reaction, on the other hand, was the most common explicitly declared reason when the lipid-lowering medication was being discontinued for a long time, and it was also more common among patients whose treatment was started after January 1, 2007.

In a multivariable analysis (table 3), patients were more likely to have their lipid-lowering medications discontinued because a change was requested by the insurance if their treatment was started before 2007 or if they had government insurance. Patients were more likely to have their lipid-lowering medication discontinued because of an adverse reaction if they had a history of adverse reactions to multiple medications, if they had started treatment before 2007, or if they were taking a nonstatin medication. Nonstatin medications were also more likely to be discontinued because of a lack of efficacy. On the other hand, patients with a history of cardiovascular comorbidities were less likely to discontinue lipid-lowering medications because of a change requested by the insurance, as were patients taking a combination of lipid-lowering medications. There was no significant relationship between CKD stage and the reason for lipid-lowering medication discontinuation.

Discussion

In this large retrospective cohort study, we have confirmed that discontinuation of lipid-lowering medications is common among patients with CKD. However, in contrast to previously published studies [9, 10] which showed that patients with more severe renal insufficiency were less likely to receive lipid-lowering therapy, we did not find a relationship between the degree of kidney failure and the rate of discontinuation of lipid-lowering medications. This could indicate that the lower rates of lipid-lowering therapy in patients with more advanced CKD are due to a difference in initiation rather than discontinuation of treatment.

Table 3. Effect of patient and medication characteristics on reasons for lipid-lowering medication discontinuation

Variable	Adverse reaction	Change requested by insurance	Ineffective	Other	Too expensive
Coronary artery disease	0.9954	**0.7559** (p = 0.0005)	1.3169	0.8814 (p = 0.01)	0.7646 (p = 0.0213)
Diabetes mellitus	1.1108	**1.8767** (p < 0.0001)	1.5156 (p = 0.0239)	**1.3734** (p < 0.0001)	1.1247
Hypertension	0.7722 (p = 0.0026)	0.8187 (p = 0.0033)	0.8343	**0.7864** (p < 0.0001)	1.0289
Cerebrovascular accident	0.8472	**0.5641** (p < 0.0001)	0.6302	**0.6910** (p < 0.0001)	0.6512 (p = 0.0257)
Peripheral vascular disease	0.8678	0.8430	1.7480 (p = 0.026)	0.9676	0.8029
Income (by USD 1,000)	1.0042 (p = 0.0271)	0.9955 (p = 0.0058)	1.0008	**1.0044** (p<0.0001)	1.0004
Age	0.9871 (p = 0.0014)	**0.9837** (p < 0.0001)	0.9805 (p = 0.0017)	0.9963	1.0111 (p = 0.0233)
History of multiple adverse reactions	**2.2178** (p < 0.0001)	1.1533 (p = 0.0456)	1.3363 (p = 0.0372)	**1.3224** (p < 0.0001)	1.2450 (p = 0.0367)
Started before 2007	**7.1225** (p < 0.0001)	**4.8321** (p < 0.0001)	**5.6271** (p < 0.0001)	**3.6238** (p < 0.0001)	**2.7541** (p < 0.0001)
CKD stage					
3B	0.9828	1.0391	0.9935	1.0893	1.0200
4	0.6692 (p = 0.0288)	0.8599	0.5638	1.1063	0.8150
5	0.3905 (p = 0.0468)	1.0767	0.5287	1.5639 (p = 0.0022)	0.9435
Gender (female)[1]	1.0185	0.9435	0.7689	**0.8575** (p = 0.0005)	0.9161
Medication class					
Nonstatin	**4.3188** (p < 0.0001)	0.9995	**7.9365** (p < 0.0001)	**4.4924** (p < 0.0001)	1.5237 (p = 0.0303)
Combo	0.6092 (p = 0.0381)	**0.1545** (p < 0.0001)	0.5691	**0.4967** (p < 0.0001)	**0.2081** (p = 0.0002)
Insurance type					
Public	1.4156 (p = 0.0007)	**1.3808** (p < 0.0001)	1.1586	**1.3487** (p < 0.0001)	1.3631 (p = 0.0124)
Other	1.5501	1.4658	0.5140	1.4230	1.7810
Race[2]					
Hispanic	0.8072	**1.6021** (p = 0.0002)	1.2167	1.1349	1.1724
African-American	0.8216	1.2864	1.2723	1.2585 0.0235	1.4064
Asian	0.7153	**2.1124** (p < 0.0001)	1.7259	1.2534	0.8248
Other	0.9692	1.2920	1.9563 0.0119	1.3219 0.0097	1.9488 0.001
Low-density lipoprotein value (by 10-unit increases)	**1.1481** (p < 0.0001)	0.9981	**1.1734** (p < 0.0001)	**1.0693** (p < 0.0001)	0.9941

Effects of variables on reasons for discontinuation are represented by odds ratios. Medications that were not discontinued served as a reference. p values <0.05 are indicated in parentheses. Statistically significant estimates after adjustment for multiple hypothesis testing are given in bold.

[1] Compared to male.

[2] Compared to Caucasians.

We found that the insurance/costs play a prominent role in changing one lipid-lowering medication for another, and that adverse reactions to medications are a common reason for long-term discontinuation of lipid-lowering medications. These findings are consistent with those of a previously published large patient survey that showed that a third of the patients switching statins did so because of costs, and nearly two thirds of the individuals who discontinued statins cited adverse reactions as the reason [23]. Both EMR data and patient surveys therefore indicate that rechallenging patients with lipid-lowering medications after reported adverse reactions, even though usually safe [16], remains uncommon.

Previously published investigations indicate that in the general population adherence to lipid-lowering medications is higher among patients who have comorbidities associated with an increase in cardiovascular risk, such as coronary artery disease, peripheral vascular disease, and stroke [13, 14, 24]. We have identified a similar relationship between comorbidities and the rates of discontinuation of lipid-lowering therapy in patients with CKD. An analysis of explicit reasons for the discontinuation showed that this relationship was mediated by both system-driven (the insurance is less likely to request a change in medications) and patient-driven (the medication is less likely to be thought too expensive) phenomena, whereas the rate of adverse reactions was similar. In contrast, there was no significant relationship between the degree of kidney failure and the rate of lipid-lowering medication discontinuation secondary to either insurance requests or unaffordability. This may be due to the risk perception by clinicians and patients, and it is consistent with the epidemiological observation that the relative additional cardiovascular risk conferred by CKD decreases with more advanced stages of renal failure [25].

A number of researchers have demonstrated gender and racial disparities in lipid-lowering therapy in the general population [26, 27]. Our study also found higher rates of discontinuation of lipid-lowering therapy among women and racial/ethnic minority patients with CKD. However, the relationship between discontinuation of lipid-lowering medications and gender lost its significance in a multivariable analysis. This may indicate that confounders, such as a lower prevalence of cardiovascular comorbidities in women, may be partially responsible for the disparity. Our findings demonstrate a higher incidence of discontinuation of lipid-lowering therapy due to insurance requests among Asians and Hispanics. However, such requests should most of the time lead to an alternative treatment rather than the complete cessation of treatment. Further research is therefore needed to better understand the origin of disparities in the treatment of dyslipidemia.

The findings of our study confirm clinical experience that adverse reactions to lipid-lowering medications are commonly reported in routine practice of medicine. On the other hand, randomized placebo-controlled trials in patients with CKD typically show minimal differences in the rates of adverse reactions to lipid-lowering therapy between active agent and placebo groups [5, 28, 29]. This difference is similar to that found in the general population [30–34]. Recent studies in the general population showed that many adverse reactions to lipid-lowering medications reported in routine medical practice may be tolerable, specific to individual agents, or not due to lipid-lowering medications at all [16]. Further studies are needed to determine whether this is also the case among patients with CKD.

Our study has several limitations. Data was collected at a single healthcare system. A significant fraction of the data (particularly explicitly documented reasons for discontinuation of lipid-lowering medications) was missing; if data was not missing at random, this could affect the analytical findings. Our sample size was too small to assess individual, nonstatin, lipid-lowering medications; therefore, they were grouped together. Relatively small numbers of patients with higher CKD stage and racial/ethnic minorities limit our ability to draw conclusions about differences in reasons for lipid-lowering medication discontinuation between these groups.

Despite the availability of advanced EMR, many discontinuations of lipid-lowering medications in our study did not have reasons documented in the structured data, and even the discontinuations themselves were not always explicitly recorded. This is consistent with prior investigations that showed that a large fraction of medical information is recorded only in narrative (e.g. provider notes) but not structured data [35–37]. While manual chart review of large numbers of records to abstract information from narrative documents is not always feasible, natural language processing technology can allow for rapid and accurate identification of critical pieces of information [38]. We have previously demonstrated that this technology can be successfully used to identify documentation of adverse reactions to medications – an important reason for their discontinuation [19]. Further research is needed to develop natural language processing tools for a comprehensive analysis of the reasons for medication discontinuation.

Our findings indicate that lipid-lowering medications are commonly discontinued in patients with CKD, frequently for prolonged periods of time. Further research is needed to ensure appropriate lipid-lowering therapy for these individuals at high cardiovascular risk.

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Disclosure Statement

The authors have no conflicts of interest to disclose.

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