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Clinical Research

Nonadherence to Statin Therapy: Discontinuation After a Single Fill

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ABSTRACT

Introduction: Adherence to statin medications is known to be suboptimal. What is less known is the rate of discontinuation immediately after therapy has been initiated. The primary objective of this study was to determine what proportion of nonadherence in the first year of statin therapy was due to discontinuation after a single fill.

Methods: We identified new statin users within low-risk (hypertension [HTN]), medium-risk (coronary heart disease [CHD]), and high-risk (heart failure [HF]) cohorts during a 9-year period. All data came from administrative health care databases.

Results: The cohorts included 9445 HTN, 1141 CHD, and 778 HF patients. At 1 year, the proportions of patients with less than 80% adherence to statin medications were 47.9% (HTN), 38.3% (CHD), and 50.0% (HF). Among all patients classified as nonadherent at 1 year, 18.0% of HTN, 16.3% of CHD, and 28.2% of HF patients had discontinued statin medications after only 1 dispensation. Within 3 months of starting statin therapy, 29.7%, 40.3%, and 47.5% of all nonadherent HTN, CHD, and HF patients, respectively, had discontinued the new statin medication. After regression analysis, the only independent covariate that was consistently associated with discontinuation after a single fill was receiving fewer medical follow-up visits.

Conclusions: Immediate discontinuation after a single fill contributes disproportionately to statin nonadherence. This suggests an important time to prevent nonadherence is within the first month of treatment initiation.

RÉSUMÉ

Introduction : L'observance du traitement par statines est considérée comme sous-optimale. Ce qui est moins connu est le taux d'abandon dès le début du traitement. L'objectif primaire de cette étude était de déterminer dans quelle proportion au cours de la première année du traitement par statines la non-observance était due à l'abandon après une seule ordonnance.

Méthodes : Nous avons identifié les nouveaux utilisateurs de statines dans les cohortes à faible risque (hypertension [HTN]), à moyen risque (maladie coronarienne [MC]) et à risque élevé (insuffisance cardiaque [IC]) durant 9 ans. Toutes les données provenaient de bases de données administratives des soins de santé.

Résultats : Les cohortes ont inclus 9445 patients ayant de l'HTN, 1141 patients ayant une MC et 778 patients ayant une IC. Après 1 année, les proportions de patients ayant moins de 80 % d'observance au traitement par statines ont été de 47,9 % (HTN), 38,3 % (MC) et 50,0 % (IC). Parmi tous les patients démontrant une non-observance au traitement après 1 année, 18,0 % des patients ayant de l'HTN, 16,3 % des patients ayant une MC et 28,2 % des patients ayant une IC ont abandonné les statines après 1 seule ordonnance. Dans les 3 mois suivant le début du traitement par statines, 29,7 %, 40,3 % et 47,5 % respectivement de tous les patients ayant de l'HTN, une MC et une IC et ayant démontré une non-observance au traitement ont abandonné la nouvelle médication par statines. Après l'analyse de régression, la seule covariable indépendante qui a constamment été associée à l'abandon du traitement après une seule ordonnance a été un moins grand nombre de visites pour le suivi médical.

Conclusions : L'abandon immédiat après une seule ordonnance contribue de manière disproportionnelle à la non-observance du traitement par statines. Ceci suggère l'importance d'intervenir au cours du premier mois de traitement pour prévenir la non-observance du traitement par statines.

The benefits of statin therapy to treat cardiovascular disease are well documented. However, these potential benefits are based on the assumption of drug adherence.[1] Although adherence to medications within randomized trials can be quite high, these rates are due mainly to highly selective patient inclusion criteria and the rigourous attention that study participants receive.[2] When these conditions are altered, adherence to chronic medications can be as low as 37% even within randomized trials.[2] When observational studies are included, as few as 25% are taking their cholesterol lowering medications in the long term.[2-4] Medication nonadherence is important because a growing body of literature is suggesting that better delivery of

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established therapies could possibly save more lives than discovering innovations.[5,6]

Although it has been demonstrated that adherence drops substantially after the first 6 months of therapy, recent studies suggest that statin nonadherence is influenced by a high rate of discontinuation (nonpersistence) immediately after therapy has been initiated.[3] For example, a secondary analysis within 1 study found that 18.5% of new statin users did not complete their second fill.[7] Another study accessing a diabetes registry found that 21.8% of those dispensed a cholesterol-lowering medication did not refill their first prescription.[8] A third study reviewing medication discontinuation after myocardial infarction (with statins being 1 of 3 medications dispensed) found that 17.9% discontinued at least 1 medication, 3.7% discontinued 2 medications, and 12.1% discontinued all 3 medications within 1 month after hospital discharge.[9]

The primary objective of our study was to determine what proportion of nonadherence in the first year of new statin therapy was due to discontinuation after only a single fill within 3 distinct cardiovascular cohorts from Saskatchewan, Canada. The second objective was to determine the rate of discontinuation occurring within 3 months of starting therapy.

Methods

Data source

All study data were provided from administrative health care databases in the province of Saskatchewan. Information is collected on physician services, hospitalizations, and vital statistics for 99% of Saskatchewan residents excluding members of the Canadian Armed Forces, the Royal Canadian Mounted Police, and federal penitentiary inmates. Medication fill information is also captured for 90% of the population as the remaining 10% (primarily Registered Indians) receive federal medication benefits.[10] Hospital discharge diagnoses were coded with *International Classification of Diseases, Ninth Revision*, before April 1, 2001, and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Clinical Modification* after April 1, 2001.[10,11] The positive predictive value for a hospital discharge diagnosis of acute myocardial infarction from a Saskatchewan administrative dataset is 0.96.[12] As such, health services information from these datasets has been published in leading journals to guide clinical decision making.[13]

Cohort definitions

We identified new statin users among 3 distinct cardiovascular-risk cohorts in Saskatchewan.[14-16]

The first cohort (hypertension [HTN]) was made up of patients who were older than 40 years and were dispensed a new prescription for an antihypertensive agent between January 1, 1994, and December 31, 2002. To capture uncomplicated cases of hypertension, patients were excluded if they were dispensed an antihypertensive agent or any other prescription (oral hypoglycemics, insulin, digoxin, antiarrhythmic drugs, or nitrates) within 5 years of study entry that would signify previous cardiovascular conditions. Patients were also excluded if they were hospitalized within 5 years of study entry for a cardiovascular event (myocardial infarction, unstable angina, congestive heart failure, stroke, other ischemic heart disease, pulmonary circulation, other heart disease, arterial disease, hypertensive disease, or procedures for percutaneous transluminal coronary angioplasty and coronary artery bypass graft).[14]

The second cohort (coronary heart disease [CHD]) was made up of patients aged between 30 and 70 years who were dispensed a new prescription for a statin (atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, or simvastatin) between January 1, 1994, and December 31, 2001. To be included, patients required an initial acute coronary syndrome hospitalization (myocardial infarction or unstable angina) or revascularization procedure (percutaneous transluminal coronary angioplasty or coronary artery bypass graft surgery). Patients were excluded if there was any cardiovascular event or use prior use of a statin medication within 5 years of study entry.[15]

The third cohort (heart failure [HF]) included patients who were newly hospitalized with a "most responsible discharge diagnosis" of heart failure between January 1, 1994, and December 31, 2003. Cohort entry date was the discharge date from the initial heart failure hospitalization. Patients were excluded if they has been hospitalized for heart failure within 5 years of study entry.[16]

For all patients we established a cohort entry date that corresponded to the qualifying event within each respective cohort. Specifically, in the HTN cohort, the cohort entry date was the date of the first fill for an antihypertensive medication, whereas the cohort entry dates for the CHD and HF cohorts were based on the date of discharge for the CHD or HF hospitalization, respectively.

In all cohorts, patients were excluded if a diagnosis of human immunodeficiency virus or indication of a solid organ transplant occurred in the 5 years prior to the first statin prescription. Patients were excluded also if they did not receive continuous benefits from Saskatchewan Health for a minimum of 5 years prior to their study entry date.

New statin use

Within each cohort, we identified patients receiving a new fill for a statin (no statin fill within previous 5-year period) any time after the initial cohort entry date. In order to ensure at least 1 year of follow-up, those who died or whose health coverage was terminated within 365 days of study entry date were excluded.

Measure of adherence

There is no single gold standard for measuring medication adherence.[2] In our study, the tablets-per-day method was used to estimate adherence at 1 year after the original statin fill. This measure is calculated by dividing the total number of tablets dispensed during the 1 year follow-up by the total number of days in the observation period (365 days).[17] This method is considered to be an accurate measure of overall adherence in closed pharmacy systems in countries that have universal drug coverage.[2] As a sensitivity measure, the fills-per-month method was also computed and compared for consistency.[14] For those hospitalized during the 1-year follow-up period, hospital duration was subtracted from the denominator because hospitalized patients receive institutional supplies of medication only.

	HTN Cohort	CHD Cohort	HF Cohort
Initial cohort sample	67,939	1,501	14,455
New statin fill No statin fills in previous 5 years Exclusions Previous CV event or hospitalization HIV, solid organ transplant No continuous benefits for 5 years	12,233	1,501	859
One year of follow-up data Exclusions Death, moved to other jurisdiction			
Final sample	9,445	1,141	778

Figure 1. Flow chart. CHD, coronary heart disease; CV, cardiovascular; HF, heart failure; HIV, human immunodeficiency virus; HTN, hypertension.

End points

The primary end point was the proportion of nonadherent patients (tablets per day ≤ 80%) obtaining only 1 fill during the entire 1-year follow-up period.[4] The secondary end point was the rate of discontinuation occurring within 3 months (102 days) of starting therapy. In our study, nonadherence included nonpersistence and poor execution. Patients who were nonadherent were followed for a second year to determine whether they restarted treatment.

Analysis

Baseline characteristics were compared with chi-square tests between those who received only 1 fill during the 1-year follow-up and those who had more than 1 fill but still had less than 80% adherence.

Information collected on factors that could impact adherence included (1) age, (2) gender, (3) comorbidity measured with a chronic disease score (CDS) based on the Von Korff methodology,[18] (4) the number of new cardiovascular medications other than statins dispensed during follow-up, (5) the number of additional noncardiovascular medications dispensed during the year of observation, (6) medical follow-up by the number of physician visits during the observation period, and (7) year of index statin fill.

A binary logistic regression model was built to describe, for all 3 cohorts, the relationship between the outcome of discontinuation after a single fill and outcomes of those who had more than 1 fill but less than 80% adherence. A hierarchal well-formulated front-wise modelling approach was used instead of a computer-generated stepwise algorithm.[19] In the final model, the unadjusted effect of each covariate was determined and then entered1 step at a time, based on changes in the −2 log likelihood and the Wald test.[20] The final regression model included factors with beta values for which the P values were < 0.05.[20] The final results were presented as adjusted odds ratios with 95% confidence intervals. All analyses were performed with an SPSS18.0 software package.

Results

The HTN cohort, the CHD cohort, and the HF cohort had 67,939, 1501, and 14,455 patients, respectively. The numbers of patients who filled a new statin prescription after the study entry date but had no fills for a statin within the previous 5-year period were 12,233 (HTN), 1501 (CHD), and 859 (HF). After excluding those without 1 full year of follow-up data, the cohorts were reduced to 9445 (HTN), 1141 (CHD), and 778 (HF) patients (Fig. 1). The mean durations of time from index date to cohort entry date were 649 days, 639 days, and 764 days, respectively.

The characteristics of the cohorts are described in Table 1. Among the cohorts, patients within the HF cohort were oldest, received the most medical follow-up visits, and were prescribed the most other cardiovascular drugs during the observation period.

At 1 year, the proportion of nonadherent patients (≤ 80% adherence by the tablets-per-day method) was 47.9% within the HTN cohort, 38.3% within the CHD cohort, and 50.0% within the HF cohort (Table 2). As a sensitivity measure, the proportion of nonadherence using the fills-per-month method was 44.7% within the HTN cohort, 39.8% within the CHD cohort, and 48.7% within the HF cohort.

Among all patients classified as nonadherent at 1 year, 18.0% of HTN, 16.3% of CHD, and 28.2% of HF patients had discontinued statin medications after only 1 fill (Table 2). When for all new users (not just nonadherent patients) are included, first fill discontinuations accounted for 8.6% (HTN), 6.2% (CHD), and 13.8% (HF). Of the patients who discontinued after the first fill and could be followed for 2 full years, 13.9% of the HTN cohort, 12.7% of the CHD cohort,

Table 1. Description of cohorts

	HTN cohort number (%)	CHD cohort number (%)	HF cohort number (%)
Age (years)			
30-39	0 (0%)	48 (3.2%)	0 (0%)
40-49	1390 (14.7%)	268 (17.9%)	28 (3.6%)
50-59	2917 (30.9%)	489 (32.6%)	95 (12.2%)
60-69	2944 (31.2%)	696 (46.4%)	231 (29.7%)
≥ 70	2194 (23.2%)	0 (0%)	424 (54.5%)
Gender			
Male	4603 (48.7%)	1154 (76.9%)	468 (60.2%)
Female	4842 (51.3%)	347 (23.1%)	310 (39.8%)
	Mean (SD)	Mean (SD)	Mean (SD)
No. medical visits during follow-up	14.1 (11.6)	12.8 (9.3)	29.5 (27.1)
No. hospitalizations during follow-up	0.2 (0.7)	1.2 (0.5)	1.1 (1.8)
No. non-CV meds during follow-up*	1.4 (1.2)	2.7 (4.6)	2.4 (1.4)
No. other CV meds during follow-up†	2.0 (0.8)	2.4 (1.2)	3.7 (0.8)
No. diabetes meds during follow-up‡	0.1 (0.3)	0.1 (0.4)	0.5 (0.5)
Von Korff chronic disease score	3.3 (1.9)	8.1 (2.9)	6.5 (3.3)

CHD, coronary heart disease; CV, cardiovascular; HF, heart failure; HTN, hypertension.

*Antidepressants, antipsychotics, oral and parenteral glucocorticosteroids, biphosphonates, uric acid agents, gastrointestinal protectant drugs, and NSAIDs.

†Antihypertensive agents, diuretics, cardiac, nonstatin lipid lowering drugs and anticoagulants.

‡Oral hypoglycemic or insulin.

and 8.4% of the HF cohort resumed treatment in the following year (Table 2).

Within 3 months (102 days) of starting statin therapy, 29.7% (HTN), 40.3% (CHD), and 47.5% (HF) of all nonadherent patients had discontinued the new statin medication. These patients made up 14.2% (HTN), 15.4% (CHD), and 24.3% (HF) of all new users of statin therapy.

Prior to statistical adjustment, a number of variables were associated with discontinuation after a single fill. Among the HTN cohort, these variables included receiving 5 or fewer medical follow-up visits during the observation period, filling 5 or more noncardiovascular medications, filling only 1 other cardiovascular medication, and having a lower score (1-2) on the CDS. For the CHD cohort, the variables included receiving 5 or fewer medical follow-up visits during the observation period and having a lower score (1-2) on the CDS. Within the HF cohort, the variables associated with discontinuation after a single fill included receiving 5 or less medical follow-up visits during the year but a higher score (≥ 5) on the CDS (Table 3).

After regression analysis, the only covariate consistently associated with discontinuation after a single fill was receiving fewer medical follow-up visits during the observation period. Using a reference category of more than 20 physician visits, receiving 5 or fewer physician visits during observation increased the odds of immediate treatment discontinuation by 57% in the HTN cohort, 136% in the CHD cohort, and 172% in the HF cohort. Being prescribed a higher (≥ 5) number of noncardiovascular medications was also significant for the HTN cohort (Table 4).

Confounding was detected only in the HTN cohort, while interaction was not detected in any model.

Conclusion

The rate of statin discontinuation immediately after therapy has been initiated appears to be a topic worthy of review. The instant nature of treatment discontinuation suggests there may be important factors that occur (or do not occur) during the process of receiving an initial prescription for a statin medication from a physician. To date, most studies have reported on nonadherence after the first 6 months of treatment.[2] Only 1 study has reported exclusively on statin first fill discontinuation within a cardiovascular cohort and found that 18.5% of all statin initiators discontinued after the first fill.[5] This finding is of greater magnitude than, yet consistent with our study.

Our finding appears to be consistent with other chronic disease medication nonadherence. A recent study found that 50% of patients were nonadherent to antihypertensives at 1 year, with 39% of the discontinuations occurring after the first fill.[21] As such, our finding appears to be more universal across chronic disease medications instead of restricted to statins alone.

Table 2. Statin adherence at 1 year and after first fill, by cohort

	HTN cohort number (%)	CHD cohort number (%)	HF cohort number (%)
	9445	1141	778
Adherence to statins at 1 year*			
80% adherence or higher	4918 (52.1%)	704 (61.7%)	389 (50.0%)
Less than 80% adherence	4527 (47.9%)	437 (38.3%)	389 (50.0%)
Nonadherent after first fill	814 of 9445 (8.6%)	71 of 1141 (6.2%)	107 of 778 (13.8%)
Among nonadherent only, % discontinuation after first fill	814 of 4527 (18.0%)	71 of 437 (16.3%)	107 of 379 (28.2%)
Continued treatment in following year	113 of 814 (13.9%)	9 of 71 (12.7%)	9 of 107 (8.4%)

CHD, coronary heart disease; HF, heart failure; HTN, hypertension.

*Adherence measured with tablets-per-day method.

Table 3. Unadjusted associations with statin discontinuation after first fill, by cohort

First fill discontinuation cross-tabulations	HTN cohort	*P* value	CHD cohort	*P* value	HF cohort	*P* value
Age (years)		0.042		0.379		0.127
30-49	10.1%		6.7%		8.2%	
50-59	8.7%		6.5%		14.6%	
60-69	8.2%		6.3%		12.2%	
≥ 70	8.1%		NA		16.6%	
Gender		0.054		0.409		0.375
Male	8.9%		6.5%		13.4%	
Female	8.3%		5.1%		14.8%	
Medical follow-up visits during year		0.000		0.015		0.000
1-5	12.8%		10.8%		34.6%	
6-10	7.9%		4.9%		21.4%	
11-20	7.6%		6.9%		6.5%	
> 20	7.9%		3.0%		13.1%	
Hospitalizations during follow-up		0.236		0.827		0.863
None	8.8%		6.7%		14.6%	
≥ 1	7.4%		7.0%		13.2%	
Non-CV fills during follow-up		0.000		0.980		0.433
0-1	7.7%		6.9%		14.2%	
2-4	9.6%		6.9%		13.1%	
≥ 5	15.4%		NA		20.8%	
Other CV fills during follow-up		0.000		0.094		0.241
1	10.3%		7.7%		17.2%	
2	8.0%		5.8%		14.6%	
3	7.3%		3.3%		13.3%	
≥ 4	9.3%		3.2%		13.8%	
Diabetes meds during follow-up		0.252		0.453		0.555
Yes	8.7%		4.9%		13.9%	
No	7.9%		6.4%		14.0%	
Von Korff chronic disease score		0.000		0.000		0.040
1-2	9.9%		23.5%		5.8%	
3-4	7.9%		16.3%		14.0%	
≥ 5	7.8%		5.6%		14.8%	
Index year		0.774		0.781		0.615
1994	9.2%		9.5%		9.3%	
1995	9.1%		6.7%		11.2%	
1996	10.8%		4.6%		8.4%	
1997	9.7%		7.1%		9.3%	
1998	8.9%		6.1%		14.0%	
1999	7.7%		4.6%		15.0%	
2000	9.1%		6.8%		13.1%	
2001	8.7%		6.0%		12.1%	

CHD, coronary heart disease; CV, cardiovascular; HF, heart failure; HTN, hypertension; NA, nonapplicable.

Comparing nonadherence among the cohorts, we determined that nonadherence was greater within the HF cohort than within the other two. This finding is inconsistent with most of the literature, which suggests patients with higher disease risk tend to adhere to chronic medications better than do groups with lesser risk.[2] This difference might be due to the age of the HF cohort, although the CHD cohort had a higher CDS.

Table 4. Adjusted associations with statin discontinuation after first fill, by cohort

	HTN cohort		CHD cohort		HF cohort	
First fill discontinuation	OR	95% CI	OR	95% CI	OR	95% CI
Medical follow-up visits*						
1-5	1.57	1.27-1.94	2.36	1.15-4.87	2.72	1.43-5.21
6-10	1.71	1.38-2.12	1.63	0.87-3.05	1.24	0.61-1.47
11-20	1.66	1.28-2.11	3.94	1.50-10.33	0.55	0.27-1.10
> 20 (reference)						
No. of non-CV medications†						
2-4	1.85	1.07-3.21	-	-	-	-
≥ 5	2.39	1.38-4.17	-	-	-	-
0-1 (reference)						
R^2	.014		.024		.071	

CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; HF, heart failure; HTN, hypertension; OR, odds ratio; hyphen (-) signifies nonimportance to model.

Reference category for dependent variable: More than 1 statin dispensation but less than 80% adherence. Reference categories for independent variables.

*More than 20 medical follow-up visits during year.

†0-1 non CV medications.

However, being prescribed more noncardiovascular medications, 1 indicator of treatment complexity and comorbidity, was associated with discontinuation after a single fill within the HTN cohort. This finding is consistent with the literature.[2,3] As well, our finding that reduced medical follow-up is associated with discontinuation is also consistent with previous reviews on drug adherence.[2,3] Regular follow-up might suggest a strong physician-patient relationship, while reduced follow-up might suggest a lesser bond or even embarrassment, given patient nonadherence. Indeed, the implementation of treatment algorithms requiring regular follow-up could be an important strategy to reduce early nonadherence and facilitate treatment goals.[22] Caution is advised given the limited ability of the regression models to explain a substantial proportion of variance.

The most often cited theoretical paradigm for chronic medication nonadherence comes from Meichenbaum and Turk.[23] This model, developed in 1987, suggests that the determinants of nonadherence to medications can be categorized into 5 groups: (1) patient factors, (2) the disease being treated, (3) conditions relative to treatment, (4) the relationship of the health care provider with the patient, and (5) clinic organization.

A systematic literature review on interventions to improve adherence to lipid-lowering medications concluded that patient reinforcement in the form of telephone reminders and pharmacist review may improve adherence.[3] However, this review also suggested that the appropriate time for intervention is after 6 months, which is consistent with the findings of another literature review on chronic medications.[2]

Our results suggests that initiating support to patients after 6 months would be too late for many individuals who have already discontinued their medication by that time.[24]

There are a number of study limitations to discuss. First, our study did not include information on important variables that can influence adherence, such as lack of patient agreement and doctor-patient relationships.[2] Second, our study does not include any information as to why statin therapy was actually prescribed or discontinued. Third, the use of an administrative dataset requires the assumption that medications that were dispensed were actually taken.

The current state of knowledge as to the appropriate time to intervene to improve adherence to statin medications appears to need updating. Our research suggests that in order to prevent discontinuation, an important time for intervention is within the first month of treatment initiation.

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