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A Competing Risks Prescription Refill Model of Compliance and Persistence

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ABSTRACT

Objectives: There is evidence to suggest that noncompliant and nonpersistent behaviors have differing risk factors, clinical consequences, and responses to intervention. This has led to calls for these behaviors to be defined and measured separately to characterize medication-taking behavior comprehensively. Current prescription refill models of compliance are, however, unable to appropriately distinguish between noncompliant and nonpersistent behaviors. To address this limitation, a prescription refill model of medication-taking behavior in which noncompliance and nonpersistence are treated as competing risks is presented.

Methods: The proposed competing risks model of compliance and persistence is compared with a selection of widely applied prescription refill models of compliance and persistence using a common cohort of patients prescribed statin therapy.

Results: The competing risks model allows the simultaneous measurement of noncompliance and nonpersistence, the partitioning of their individual contributions to medication-taking behavior, and the estimation of noncompliance risk for patients with varying treatment persistence. The results from this model provide information about the relative and overall contributions of noncompliant and nonpersistent behaviors to medication-taking behavior. The methodology also allows an assessment of the differential influence of various risk factors on these behaviors.

Conclusions: The proposed competing risks model differentiates between noncompliant and nonpersistent behaviors using prescription refill data. Results from the model provide insights into the dynamics of noncompliant and nonpersistent behaviors that have not been possible with current prescription refill methodologies.

Keywords: competing risks, compliance, persistence, prescription refill, statins.

Introduction

Medication taking can be defined in terms of two distinct behaviors: the length of time from initiation to discontinuation of treatment—persistence; and the quality of treatment execution during that time—compliance [1–3]. This distinction between compliance and persistence implies that the quality of a patient's treatment execution can only be evaluated with respect to the length of time that he/she is actively engaged in taking treatment [1]. The extent to which a patient would act in accordance with the prescribed interval and dosage of a treatment regimen cannot be measured after that treatment has been discontinued and periods of treatment nonpersistence should not therefore be considered part of a patient's compliance behavior. The partitioning of medication taking into compliance and persistence is supported by evidence indicating that the risk factors [4] and clinical consequences [5,6] of the two behaviors differ. There is also evidence to suggest that interventions to improve medication-taking behavior can have a differing impact on compliance and persistence [7]. These characteristics have led to the recommendation that compliance and persistence should be defined and measured separately [1,8–10].

Prescription refill records are an invaluable resource for the assessment of medication-taking behaviors in large numbers of patients over extended periods of time. The use and validity of prescription refill records for the measurement of compliance have, however, been the subject of a number of recent criticisms [11,12]. The most significant of these is the contention that prescription refill records are unsuitable for the measurement of compliance because they are unable to provide the necessary distinction between noncompliant and nonpersistent behaviors. These criticisms are based upon the observation that current prescription refill models of compliance allow the inclusion of periods of treatment nonpersistence in their estimates of compliant behavior [13–15]. This results in the underestimation of compliance for nonpersistent patients and has led to the belief that compliance with many treatments is as low as 50% to 60% [16]. In addition, as compliance rates are underestimated specifically for nonpersistent patients, estimates of noncompliance risk obtained from these prescription refill models are biased for covariates associated with nonpersistence risk [14,15].

The evaluation of compliance behavior with respect to the length of time that a patient persists with treatment is difficult with current compliance models because they are unable to adequately account for the dependent nature of noncompliant and nonpersistent behaviors and the systematic variations in treatment duration this produces. To address these limitations, this article presents a prescription refill model of medication-taking behavior in which established measures of noncompliance and nonpersistence are modeled as competing risks. The use of a competing risks model is appropriate in situations where more than one type of event plays a role in failure and these events are not independent, i.e., the occurrence of one event either precludes or significantly alters the probability of the other [17]. This applies to the medication-taking process, where patients taking a treatment are at simultaneous risk of both nonpersistence and noncompliance; with the occurrence of either behavior signifying a failure to take the treatment correctly although, respectively, precluding or modifying the risk of the competing behavior. Nonpersistence precludes the subsequent occurrence of noncompliance, because it is not possible for a patient to exhibit noncompliant behavior with a treatment he/she is no longer taking

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[1], whereas noncompliance increases the probability that a patient will subsequently become nonpersistent [12]. The proposed competing risks model appropriately accounts for the dependence between noncompliant and nonpersistent behaviors by changing the focus of analysis away from making inferences about the risk of noncompliance occurring in patients who are compliant, toward making inferences about the risk of noncompliance occurring in patients who are both compliant and persistent [17]. To illustrate this, the competing risks model is compared with a number of commonly applied prescription refill models of compliance and persistence, using a cohort of patients prescribed statin therapy.

Methods

Source of Data

Prescription refill data was obtained from the Irish Health Care Executive, Primary Care Reimbursement Services (HSE-PCRS) database. This database records information on prescriptions dispensed to patients with eligibility for the General Medical Services (GMS) health-care scheme. The GMS provides free health-care services, including the provision of medicines, to patients over the age of 70 and patients who are unable without undue hardship to arrange primary health-care services. Approximately one-third (1.27 million) of the Irish population were registered for this scheme in 2007.

Study Cohort and Covariates

All patients over the age of 16, commencing a statin (simvastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, combined simvastatin/ezetimibe) as initial antihyperlipidemic treatment between the January 1, 2004 and January 2, 2006 were identified from the HSE-PCRS database. The date of the first prescription for a statin during this period was identified as the index date for each patient. Commencing statin treatment was defined as having no statin prescribed in the 365 days before the index date. Initial treatment with a statin was defined as having no other antihyperlipidemic treatment prescribed in the 365 days before the index date. Prescription refill data were available from January 1, 2003 to June 30, 2007. Information on loss of eligibility for the GMS scheme or death was not available and patients were instead considered lost to follow-up from the date they received their last prescription for any type of medication.

A longitudinal data set of statin prescription refills was assembled for each patient in the study cohort by assigning the days' supply from each prescription to sequential days from the date of dispensing [18]. Prescriptions refilled before the assigned daily supply from previous prescriptions being exhausted were handled in the following way: where an overlapping prescription was for the same statin type, the days' supply was appended to the last assigned day of the previous prescription; where the overlapping prescription was for a different statin type, indicating a treatment switch, the days' supply remaining from previous prescriptions was discarded. These longitudinal prescription refill histories were used in all of the compliance and persistence models described next.

Covariates previously associated with statin noncompliance were selected for inclusion in the prescription refill models. These included gender, age, statin type, and initial prescriber of current statin (community or hospital). The presence of certain comorbidities was also identified using the prescription of specific drugs as a surrogate marker for disease. Ischemic heart disease (IHD) was identified by the presence of a prescription for a nitrate [19] or potassium channel activator. Diabetes was identified by the presence of a prescription for an oral antidiabetic medication or insulin. Diagnoses of depression or Alzheimer's disease were identified by the presence of a prescription for an antidepressant or anti-Alzheimer medication, respectively.

Standard Models of Compliance and Persistence

Three types of compliance model, commonly applied to prescription refill data, were identified from the literature. There has been no published taxonomy of these models and they are referred to here according to their general properties as single measure, repeated measure, and time to noncompliance models.

Medication-taking behavior analyses based on the calculation of a single measure of compliance over a specified observation period are the most frequently utilized models for the assessment of compliance with prescription refill data [13,20]. A variety of techniques have been proposed for the measurement of compliance in these single measure models [20]. The medication possession ratio (MPR) technique, recommended in the reviews by Halpern et al. and Peterson et al. was used in this model [9,14]. Compliance rates were calculated for the single measure model by dividing the number of days between the start of a patient's first and last prescription refills, up to a maximum of 720 days, into the number of daily doses assigned to that treatment interval. The MPR technique cannot be used to calculate compliance rates for patients receiving fewer than two prescriptions and these patients were excluded from the single measure model. Patients were defined as noncompliant in the single measure model if they had a compliance rate of less than 80%.

Repeated measure models of compliance are based upon the periodic calculation of a patient's compliance over consecutive intervals of a defined length [14]. A variety of interval lengths has been used in the past with little objective rationale given for their selection [18,21–25]. The most frequently used interval length of 90 days was selected for use in this model. This represents three times the average length of a statin prescription in the HSE-PCRS database. Compliance rates were calculated for each complete consecutive 90-day interval in a patient's follow-up by dividing the number of daily doses assigned to each interval by 90. Compliance rates could not be calculated for patients with less than 90 days' follow-up and these patients were excluded from the repeated measure model. Patients were defined as noncompliant in any given 90-day interval if they had a compliance rate of less than 80% for that interval.

Time to noncompliance models provide an estimation of the length of time a patient can be expected to take a medication at or above a certain intensity [26–28]; where the intensity can be defined in terms of both the level of noncompliance and the length of the noncompliant episode. In this study, compliance rates were calculated for every day in a patient's follow-up by dividing the number of days between treatment initiation and each day, into the number of daily doses assigned to that treatment interval. For example: a patient's compliance rate at day 40 was calculated by dividing the number of days from treatment initiation into the number of doses assigned to that 40-day treatment interval. This calculation was repeated for every day in a patient's follow-up. Patients were defined as noncompliant if their compliance rate dropped below 80% for at least 180 consecutive days. The time to noncompliance was defined as the length of time from treatment initiation to the first day of this noncompliant episode. Patients who became lost to follow-up during the defined noncompliant episode length were identified as lost to follow-up instead.

Persistence with statin therapy was also measured using a standard permissible gap model [13]. Patients were identified as

nonpersistent if the number of consecutive days without an assigned statin dose exceeded a permissible gap of 180 days. The time to nonpersistence was taken as the length of time from treatment initiation to the first day of the defined permissible gap. Patients who became lost to follow-up during the defined nonpersistent episode length were identified as lost to follow-up instead.

Competing Risks Model of Compliance and Persistence

In the competing risks model of medication-taking behavior, noncompliance and nonpersistence are treated as separate events, with the earliest occurrence of either identified as the defining event for each patient. This approach ensures that only noncompliant events occurring during the time that a patient persists with treatment are considered part of a patient's compliance behavior. For this study, time to noncompliance and time to nonpersistence were measured using the standard definitions and established techniques described previously. Noncompliant events were defined as a compliance rate of less than 80% for at least 180 consecutive days. Nonpersistent events were defined as a permissible gap in treatment of at least 180 consecutive days. Patients who became nonpersistent during the defined 180-day noncompliance episode were identified as nonpersistent instead (i.e., for a patient to be considered noncompliant, his/her compliance rate must have dropped below 80% for 180 consecutive days, but he/she could not become nonpersistent during this 180-day period).

In addition to modeling noncompliance and nonpersistence as separate competing risks, these two events were combined into a single composite outcome to allow assessment of their joint contribution to medication-taking behavior. In this composite model, the time to either noncompliance or nonpersistence, as identified in the competing risks model described previously, was taken as the time to event for each patient.

Sensitivity Analyses

A sensitivity analysis was undertaken to confirm the robustness of the competing risks model to variations in the permissible gap length (90 days and 360 days). The single measure model of compliance was also repeated with the more commonly used, shorter maximum patient follow-up of 360 days.

Statistical Analysis

Compliance rates from the single measure model were dichotomized into compliant (≥80%) or noncompliant (<80%). A multiple logistic regression analysis was used to estimate noncompliance odds ratios with 95% confidence intervals for each covariate. Compliance rates from the repeated measure model were also dichotomized into compliant (≥80%) and noncompliant (<80%). A multivariate generalized estimating equation (GEE) model with a binomial variance distribution, a common logit link function, and an unstructured correlation matrix was used to estimate noncompliance odds ratios with 95% confidence intervals for each covariate. Results from the time to noncompliance model, the time to nonpersistence model, and the composite competing risks model were analyzed as follows. A Kaplan–Meier plot was constructed to estimate the cumulative probability of an event and a multiple Cox regression model was used to estimate hazard ratios with 95% confidence intervals for covariates in each model. Observations were censored at the time of an event, loss to follow-up or end of follow-up, whichever occurred first. Where possible covariates were treated as time-varying in analyses, otherwise baseline values at treatment initiation were used.

Cumulative incidence functions [29] for the individual competing risks of noncompliance and nonpersistence were estimated using the SAS® macro *incid*. [30] Observations were censored at loss to follow-up or end of follow-up, whichever occurred first. Multiple regression models based on the competing risk cumulative incidence functions were constructed using the pseudo-value approach developed by Andersen, Klein and Rosthøj [31,32]. This technique allows the direct regression modeling of the cumulative incidence function using pseudo-values based on the difference between the complete sample and the "*leave-one-out*" estimators of relevant survival quantities (jack-knife procedure) [32]. The pseudo-values for the competing risks cumulative incidence functions were calculated using the SAS macros *pseudoci* [33] and *cuminc* [33]. To accommodate the large sample size, only data relevant to the individual jack-knife procedure were derived at each iteration. Time-dependent covariates were incorporated into the model by prespecifying a series of time points for the calculation of corresponding pseudo-values [32,34]. The calculated pseudo-values were used as the dependent variable in GEE regression analyses for the competing risks. The distribution for these GEE models was specified as normal, the link function was the complementary log–log function, and the correlation structure was specified as independent [32,35]. The complementary log–log function gives a proportional hazards representation when applied to a survival function [35,36], allowing the exponentiated β regression coefficients from the GEE model to be interpreted as hazard ratios with 95% confidence intervals, or more appropriately as sub-distribution hazard ratios [36]. Detailed descriptions of the pseudo-value methodology and guides to the application of the SAS macros have been published by Klein et al. [32,35], Anderson et al. [31] and Rosthøj et al. [37]. SAS versions 9.1.2 and 9.2 (SAS Institute, Cary, NC) were used for all analyses and significance at $P < 0.05$ was assumed.

Results

Study Cohort

A cohort of 79,364 patients aged 16 years or older, commencing a statin as initial antihyperlipidemic treatment was identified (see Table 1). Females accounted for 55.6% of the study cohort and 62.5% of patients were aged 65 years or over at treatment initiation. Atorvastatin represented 60.3% of initial prescriptions, with 16% of patients receiving two or more different statins. The proportion of patients excluded from the single measure and repeated measure compliance models because of insufficient prescription refills or follow-up was 11.4% and 4.1%, respectively. The characteristics of these abridged cohorts are also presented.

Noncompliance and Nonpersistence Models

A selection of noncompliance and nonpersistence estimates from the competing risks and standard prescription refill models are presented in Table 2. Cumulative incidence plots for the individual and composite competing risks models are also shown in Figure 1. As expected, the separation of noncompliant and nonpersistent behaviors in the competing risks model produces noncompliance rate estimates that are considerably lower than those obtained from the three standard models of noncompliance. At 720 days' poststatin, initiation the proportion of patients identified as noncompliant in the competing risks model was 24.7% versus 37.6%, 47.3% and 52.6% in the single measure, repeated measure, and time to noncompliance models, respectively.

Table 1 Baseline characteristics of the full study cohort and the study cohort subsets used in single measure and repeated measure compliance models

	Full cohort*† (%)		Single measure model cohort‡ (%)		Repeated measure model cohort§ (%)	
N	79,364	—	70,351	—	76,119	—
Gender						
Male	35,265	(44.4)	31,137	(44.3)	33,646	(44.2)
Female	44,099	(55.6)	39,214	(55.8)	42,473	(55.8)
Age						
16–34	2,666	(3.4)	1,260	(1.8)	2,118	(2.8)
35–44	3,676	(4.6)	2,776	(3.9)	3,384	(4.4)
45–54	8,576	(10.8)	7,459	(10.6)	8,199	(10.8)
55–64	14,864	(18.7)	13,615	(19.4)	14,424	(18.9)
65–74	25,382	(32.0)	23,580	(33.5)	24,821	(32.6)
≥75	24,200	(30.5)	21,661	(30.8)	23,173	(30.4)
Statin type						
Simvastatin	4,553	(5.7)	3,954	(5.6)	4,336	(5.7)
Pravastatin	17,085	(21.5)	14,687	(20.9)	16,284	(21.4)
Fluvastatin	1,375	(1.7)	1,128	(1.6)	1,307	(1.7)
Atorvastatin	47,881	(60.3)	42,952	(61.1)	45,988	(60.4)
Rosuvastatin	8,145	(10.3)	7,344	(10.4)	7,891	(10.4)
Sim/Eze	325	(0.4)	286	(0.4)	313	(0.4)
Prescriber						
Community	71,841	(90.5)	63,307	(90.0)	69,030	(90.7)
Hospital	7,523	(9.5)	7,044	(10.0)	7,089	(9.3)
Comorbidities						
IHD	7,413	(9.3)	6,901	(9.8)	10,514	(13.8)
Diabetes	8,852	(10.8)	8,043	(11.4)	11,038	(14.5)
Depression	17,159	(21.6)	15,152	(21.5)	18,371	(24.1)
Alzheimer's disease	1,117	(1.4)	963	(1.4)	1,476	(1.9)

*The full study cohort was not eligible for use in the single measure and repeated measure models.
†Baseline values at treatment initiation.
‡Baseline values at end of first compliance calculation interval.
‡Single measure model of compliance estimated at 720 days follow-up or last statin prescription.
§Repeated measure model of compliance estimated over consecutive 90-day compliance calculation intervals.
IHD, ischemic heart disease; N, number of patients in cohort; Sim/Eze, simvastatin/ezetimibe combination.

Results from the multiple regression analyses for the competing risks and standard prescription refill models are presented in Table 3. A comparison of these results reveals that noncompliance risk estimates for a number of covariates, e.g., age, statin type and certain comorbidities, differ substantially between the competing risks and standard compliance models. In the three standard compliance models, noncompliance risk decreased with increasing age and there was a reduced risk of noncompliance in patients treated for IHD or diabetes. Noncompliance risk was also lower in patients prescribed atorvastatin, rosuvastatin, or the simvastatin/ezetimibe combination; whereas the use of fluvastatin was associated with an increased risk of noncompliance. These risk estimates are similar to those observed in previously published prescription refill studies of statin compliance [22,23,38]. In the competing risks model, however, noncompliance risk increased with age up to the 45–54 years age category, decreasing thereafter. Treatment for IHD or diabetes was associated with little or no reduction in the risk of noncompliance and there was no difference in noncompliance risk between statin types, with the exception of the simvastatin/ezetimibe combination.

In comparison to the standard permissible gap model of nonpersistence, the proportion of patients identified as nonpersistent and the distribution of nonpersistence risk remained largely unchanged in the competing risks model (see Tables 2 and 3). At 720 days after treatment initiation, 28.3% of patients were identified as nonpersistent in the competing risks model versus 32.6% in the standard permissible gap model. Increasing age, the presence of ischemic heart disease or diabetes, the use of atorvastatin or rosuvastatin, and the initiation of treatment by a hospital prescriber remained significant predictors of persistence. It is also interesting to note that the covariate risk estimates for the composite outcome of noncompliance/nonpersistence in the competing risks model are remarkably similar to those obtained from the three standard models of compliance.

Sensitivity Analyses

Cumulative incidence and covariate risk estimates from sensitivity analyses assessing the influence of permissible gap length on the competing risks model are presented in Tables A1 and A2, respectively (see appendix at: http://www.ispor.org/Publications/value/ViHsupplementary/ViH13i6_Barron.asp). Varying the length of permissible gap between 90 and 360 days changed the relative proportion of noncompliant and nonpersistent events but had little effect on the number of composite events (noncompliance and nonpersistence). This is because patients were in general reclassified from nonpersistent to noncompliant or vice versa as the permissible gap length increased or decreased. Despite these variations in the proportions of noncompliant and nonpersistent events, there was minimal change in covariate risk estimates, suggesting that the competing risks model is robust to variations in the permissible gap length used to define nonpersistence. In the single measure model sensitivity analysis, the use of a shorter maximum patient follow-up of 360 days produced little variation in the noncompliance rate estimate or the covariate risk estimates obtained.

Discussion

The competing risks model of medication-taking behavior presented in this article is the first to differentiate between noncompliant and nonpersistent behaviors using prescription refill data. The results provide important insights into the dynamics of these behaviors that have not been possible with current prescription refill methodologies.

Table 2 Selected rate or cumulative probability/incidence estimates for statin noncompliance and nonpersistence from standard and competing risk models of medication-taking behaviour

	Single measure model of compliance*	Repeated measure model of compliance†	Time to noncompliance model‡	Competing risks model of noncompliance, nonpersistence, and composite outcome§			Permissible gap model of persistence‖
Day	Noncompliance %¶	Noncompliance %¶	Noncompliance % (95% CI)#	Noncompliance % (95% CI)#	Composite % (95% CI)#	Nonpersistence % (95% CI)#	Nonpersistence % (95% CI)#
30	—	—	2.2 (2.1, 2.3)	0.9 (0.8, 0.9)	14.1 (13.8, 14.3)	13.2 (13.0, 13.4)	13.2 (13.0, 13.4)
60	—	—	27.4 (27.0, 27.7)	10.8 (10.6, 11.0)	25.9 (25.6, 26.2)	15.1 (14.9, 15.4)	15.1 (14.9, 15.4)
90	—	44.0	33.3 (32.9, 33.6)	14.9 (13.7, 14.2)	31.2 (30.9, 31.6)	17.3 (17.0, 17.5)	17.3 (17.0, 17.5)
180	—	47.8	41.0 (40.7, 41.4)	18.3 (18.1, 18.6)	40.2 (39.8, 40.5)	21.8 (21.5, 22.1)	21.8 (21.5, 22.1)
270	—	47.4	44.9 (44.5, 45.3)	20.6 (20.3, 20.9)	45.0 (44.6, 54.3)	24.4 (24.1, 24.7)	24.9 (24.6, 25.2)
360	—	49.3	47.7 (47.3, 48.0)	22.3 (22.0, 22.6)	47.9 (47.5, 48.3)	25.6 (25.3, 25.9)	27.1 (26.7, 27.4)
450	—	45.4	49.3 (48.9, 49.6)	23.1 (22.8, 23.4)	49.6 (49.2, 49.9)	26.5 (26.1, 26.8)	28.8 (28.5, 29.1)
540	—	45.6	50.7 (50.3, 51.0)	23.8 (23.5, 24.2)	51.0 (50.6, 51.4)	27.2 (26.8, 27.5)	30.3 (30.0, 30.6)
630	—	45.3	51.7 (51.3, 52.0)	24.3 (24.0, 24.6)	52.1 (51.7, 52.5)	27.8 (27.4, 28.1)	31.5 (31.1, 31.9)
720	37.6	47.3	52.6 (52.2, 53.0)	24.7 (24.4, 25.1)	53.0 (52.6, 53.4)	28.3 (27.9, 28.6)	32.6 (32.2, 32.9)
810	—	47.3	53.5 (53.0, 53.9)	25.2 (24.8, 25.5)	53.9 (53.5, 54.3)	28.7 (28.3, 29.0)	33.5 (33.1, 33.9)
900	—	40.8	54.0 (53.7, 54.3)	25.5 (25.1, 25.9)	54.5 (54.0, 54.9)	29.0 (28.6, 29.4)	34.1 (33.6, 34.6)

*Single measure model with noncompliance defined as compliance less than 80% at 720 days follow-up or last statin prescription.
†Repeated measure model with noncompliance defined as compliance less than 80% over consecutive 90-day intervals.
‡Time to noncompliance model with noncompliance defined as compliance less than 80% for at least 180 consecutive days.
§Competing risks model of compliance and persistence, with noncompliance defined as compliance less than 80% for at least 180 consecutive days and nonpersistence defined as a gap in prescription refills of at least 180 consecutive days.
‖Time to nonpersistence model with nonpersistence defined as a gap in prescription refills of at least 180 consecutive days.
¶Rate estimates expressed as %.
#Cumulative probability/incidence estimates expressed as %.
Day, number of days from statin treatment initiation; 95% CI, 95% confidence interval.

There are a number of considerations which must be taken into account when interpreting results from the competing risks model. Firstly, cumulative incidence estimates of noncompliance are interpretable as the probability of a patient becoming noncompliant at a specified time, given that the patient was both compliant and persistent up to that time. The competing risks regression estimates for noncompliance must consequently be interpreted as part of an overall assessment of the relative and combined contributions of noncompliance and nonpersistence to medication-taking behavior. Secondly, the results reflect an assessment of medication taking behavior within a single treatment episode (initiation to nonpersistence). Thirdly the competing risks model makes no assumptions about the relationship, i.e., independence, between noncompliant and nonpersistent behaviors. It is therefore incorrect to assume that upon the removal of one cause of failure, the risk of failure from other causes will remain unchanged.

Results from the competing risks model indicate that noncompliant behavior with statin therapy is not as prevalent as previously suggested [22,23,38]. Noncompliance estimates from the competing risks model are in fact comparable to those obtained from studies using "gold standard" compliance measurement techniques such as electronic medication event monitors [39,40]. These studies have reported statin noncompliance rates, exclusive of treatment nonpersistence, of 15.7% at 6 months. The cumulative incidence of noncompliance in the competing risks model at 6 months was 18.3% (Table 2). Nevertheless, more than half (53.0%) of patients commenced on statin therapy will have experienced either a noncompliant (24.7%) or a nonpersistent (28.3%) event within 720 days of starting treatment (see Table 2).

In comparison to regression estimates from the standard compliance and persistence models, results from the competing risks regression analyses allow a more detailed interpretation of the differential influence of various risk factors on noncompliant and nonpersistent behaviors. For example, results from the standard compliance and persistence models demonstrate a reduced risk of noncompliance and nonpersistence in patients receiving treatment for diabetes. Nevertheless, the separation of nonpersistent behavior from compliance estimates in the competing risks model reveals that there is in fact no difference in compliance behavior between patients with or without diabetes; although patients with diabetes do have a reduced risk of nonpersistence (see Table 3). Similar results are observed for statin type, where regression estimates from the standard compliance models suggest that there are considerable differences in compliance behavior between a number of the statins. In contrast, results from the competing risks model demonstrate that although there are differences in persistence behavior between the various statins, there is little difference in compliance behavior.

Regression estimates from the competing risks analyses suggest that much of the reported variation in statin noncompliance risk from standard compliance models is in fact attributable to differences in persistence behavior. It is recognized that standard models of compliance that do not exclude periods of treatment nonpersistence from compliance estimates can be thought of as representing both noncompliant and nonpersistent behaviors in a single hybrid or composite estimate of medication-taking behavior [14,15], with the risk assigned to covariates in predictive models reflecting the combined risk for either of these behaviors. This is confirmed by the similarity between results obtained from the three standard compliance models and the composite noncompliance/nonpersistence competing risks model (see Tables 2 and 3). Nevertheless, as demonstrated previously, the appropriate interpretation of these composite medication-

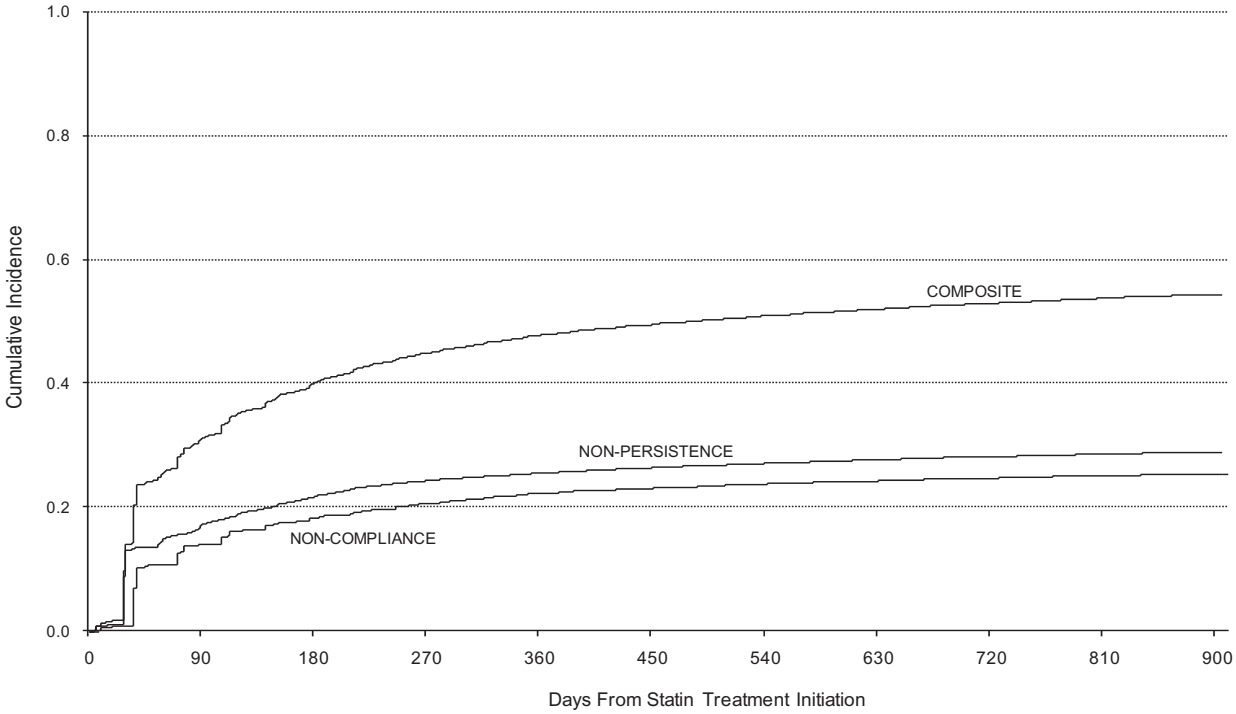

Figure 1 Competing risks cumulative incidence plot of statin noncompliance, statin nonpersistence, and composite statin noncompliance/nonpersistence.

taking behavior estimates is difficult without knowledge of the individual contributions of their component parts.

In addition to yielding information lacking from traditional methods about the dynamics of medication-taking behaviors, the competing risks model may also be of use in clinical practice. Sensitivity analyses indicate that the use of permissible gaps as short as 90 days to define nonpersistence is possible. This allows the provision of timely data on medication-taking behavior to guide the use of behavior-specific interventions. The ability to distinguish between those who do not take their treatment correctly and those who do not take it at all, in conjunction with a knowledge of the timing and specific risk factors for each behavior, provides important information for the targeting and tailoring of effective interventions [7]. Nonpersistent patients may require interventions aimed at influencing their perceptions about the risks and benefits of treatment [41]; whereas, noncompliant patients have at least acknowledged the need for treatment and may instead require interventions aimed at facilitating the integration of dosing into their daily routine [42,43]. It is also worthwhile noting the timing of nonadherent and nonpersistent events, the majority of which occur after the filling of a single prescription or within the first 90 days of treatment (see Fig. 1). This suggests that interventions timed to coincide with the initiation of treatment and the following months may provide the most benefit.

Distinguishing between noncompliance and nonpersistence also has implications for studies assessing the impact of medication-taking behaviors on treatment outcomes. Studies of "*on treatment*" efficacy have generally concluded that statin compliance rates of 80% are required for optimal outcomes [44–49]. The majority of these studies do not, however, distinguish between noncompliant and nonpersistent behaviors in their analyses. It is therefore possible that the level of statin compliance necessary for optimal efficacy is overestimated for patients who are persistent with treatment. This observation is supported by clinical trials indicating that statins have the ability to maintain efficacy with alternate day, twice weekly, or even once weekly dosing [6,50–53]; whereas periods of statin nonpersistence of as little as 90 days can significantly reduce treatment efficacy [5,54].

It is still possible and not incorrect to continue modeling nonpersistent behavior using standard time to event models. The competing risks model does, however, provide a different perspective on the analysis of persistence behavior by allowing the assessment of nonpersistence risk specifically in patients who are compliant with treatment. Nonpersistence models with similar intent to this but different methodology have been published [12]. In these studies, noncompliance was included as a time-dependent covariate in time to nonpersistence models, giving what can be considered a bidirectional noncompliance/nonpersistence multistate model [17]. The advantage of this approach for the analysis of nonpersistence is that it allows the assessment of nonpersistence risk beyond the first noncompliant episode.

In addition to the well-recognized limitations of retrospective databases and prescription refill data for the analysis of medication-taking behavior [14,20,55], there are a number of limitations specific to the competing risks model presented here. Firstly, as the competing risks model makes no assumptions about the correlation between noncompliant and nonpersistent behaviors, the interpretation of covariate risk estimates from the competing risks regression analyses requires some care. Secondly, as with all prescription refill models of medication-taking behavior, the parameters selected to define noncompliant and nonpersistent behaviors have the potential to influence the results obtained. In the competing risks model, the length of permissible gap used to define nonpersistence simultaneously defines the minimum gap between prescription refills that is considered nonpersistence and the maximum gap between prescription refills

Table 3 Adjusted odds ratio and hazard ratio estimates for statin noncompliance and nonpersistence from standard and competing risk multivariate models of medication-taking behaviour

	Single measure model of compliance*	Repeated measure model of compliance†	Time to noncompliance model‡	Competing risks model of noncompliance, nonpersistence, and composite outcome§			Permissible gap model of persistence‖
	OR (95% CI)	OR (95% CI)	HR (95% CI)	Noncompliance HR (95% CI)¶	Composite HR (95% CI)	Nonpersistence HR (95% CI)¶	HR (95% CI)
Gender							
Male	0.96 (0.93, 0.99)	1.01 (0.99, 1.03)	0.99 (0.97, 1.01)	0.97 (0.94, 1.00)	0.99 (0.97, 1.01)	1.03 (1.00, 1.06)	1.01 (0.98, 1.04)
Female	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Age (years)							
16–34	2.46 (2.19, 2.75)	4.02 (3.64, 4.44)	2.80 (2.66, 2.95)	0.74 (0.66, 0.82)	3.02 (2.86, 3.18)	3.27 (3.05, 3.51)	4.35 (4.10, 4.62)
35–44	2.30 (2.12, 2.49)	2.30 (2.17, 2.43)	1.91 (1.82, 2.00)	1.00 (0.93, 1.08)	1.91 (1.83, 2.00)	2.17 (2.05, 2.30)	2.31 (2.18, 2.45)
45–54	1.83 (1.73, 1.93)	1.55 (1.49, 1.61)	1.48 (1.43, 1.54)	1.28 (1.22, 1.34)	1.48 (1.43, 1.53)	1.41 (1.34, 1.47)	1.50 (1.43, 1.57)
55–64	1.24 (1.19, 1.30)	1.12 (1.09, 1.15)	1.14 (1.11, 1.18)	1.12 (1.08, 1.17)	1.14 (1.11, 1.18)	1.05 (1.01, 1.10)	1.14 (1.10, 1.19)
65–74	Ref	Ref	Ref	Ref	Ref	Ref	Ref
≥75	0.98 (0.94, 1.02)	1.03 (1.00, 1.05)	1.07 (1.04, 1.10)	0.92 (0.89, 0.96)	1.07 (1.04, 1.10)	1.11 (1.07, 1.15)	1.20 (1.16, 1.24)
Statin							
Simvastatin	1.02 (0.95, 1.10)	0.99 (0.94, 1.04)	0.98 (0.94, 1.03)	1.04 (0.97, 1.11)	0.99 (0.94, 1.03)	0.94 (0.89, 1.00)	0.97 (0.91, 1.02)
Pravastatin	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Fluvastatin	1.15 (1.02, 1.30)	1.19 (1.09, 1.30)	1.21 (1.13, 1.30)	0.98 (0.88, 1.10)	1.21 (1.13, 1.30)	1.27 (1.16, 1.40)	1.31 (1.20, 1.44)
Atorvastatin	0.88 (0.85, 0.92)	0.87 (0.84, 0.89)	0.88 (0.86, 0.90)	0.98 (0.95, 1.02)	0.88 (0.86, 0.90)	0.83 (0.80, 0.86)	0.86 (0.83, 0.89)
Rosuvastatin	0.97 (0.92, 1.03)	0.90 (0.87, 0.94)	0.93 (0.90, 0.97)	1.07 (1.00, 1.12)	0.93 (0.89, 0.96)	0.84 (0.80, 0.88)	0.90 (0.86, 0.95)
Sim/Eze	0.96 (0.75, 1.22)	0.71 (0.62, 0.82)	0.95 (0.82, 1.10)	1.28 (1.12, 1.45)	0.94 (0.81, 1.09)	0.76 (0.66, 0.88)	0.93 (0.77, 1.13)
Prescriber							
Community	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Hospital	0.78 (0.74, 0.82)	0.87 (0.84, 0.90)	0.86 (0.83, 0.89)	0.86 (0.81, 0.90)	0.86 (0.82, 0.89)	0.87 (0.82, 0.91)	0.86 (0.82, 0.90)
Comorbidity							
IHD	0.84 (0.80, 0.89)	0.79 (0.77, 0.82)	0.82 (0.79, 0.84)	0.94 (0.90, 0.98)	0.83 (0.80, 0.85)	0.78 (0.75, 0.81)	0.84 (0.81, 0.88)
Diabetes	0.79 (0.75, 0.83)	0.77 (0.75, 0.79)	0.82 (0.80, 0.85)	0.99 (0.95, 1.03)	0.82 (0.80, 0.85)	0.74 (0.71, 0.77)	0.76 (0.73, 0.79)
Depression	0.95 (0.91, 0.98)	1.03 (1.01, 1.06)	1.02 (1.00, 1.04)	0.96 (0.93, 0.99)	1.03 (1.01, 1.06)	1.12 (1.08, 1.15)	1.12 (1.09, 1.15)
Alzheimer's	1.09 (0.95, 1.25)	1.04 (0.98, 1.11)	1.02 (0.95, 1.10)	1.06 (0.97, 1.15)	1.03 (0.96, 1.11)	1.00 (0.92, 1.08)	1.04 (0.95, 1.14)

*Single measure model with noncompliance defined as compliance less than 80% at 720 days follow-up or last statin prescription.
†Repeated measure model with noncompliance defined as compliance less than 80% over consecutive 90-day intervals.
‡Time to noncompliance model with noncompliance defined as compliance less than 80% for at least 180 consecutive days.
§Competing risks model of compliance and persistence, with noncompliance defined as compliance less than 80% for at least 180 consecutive days and nonpersistence defined as a gap in prescription refills of at least 180 consecutive days.
‖Time to nonpersistence model with nonpersistence defined as a gap in prescription refills of at least 180 consecutive days.
¶Subdistribution hazard ratio.
95% CI, 95% confidence interval; HR, hazard ratio; IHD, ischemic heart disease; OR, odds ratio; Ref, reference category; Sim/Eze, simvastatin/ezetimibe combination.

that is considered noncompliance. Although sensitivity analyses indicate that the covariate risk estimates from the competing risks model are robust to the specification of a permissible gap length, the relative proportion of noncompliant and nonpersistent events does vary. Efforts should be made to select a permissible gap length that reflects the minimum period of medication disuse that distinguishes nonpersistent behavior (i.e., an intention to discontinue treatment) from noncompliant behavior [9]. Sensitivity analyses should also be carried out in situations where a clinically appropriate compliance rate cutoff cannot be identified.

In conclusion, the competing risks model described in this article addresses a number of the limitations of standard prescription refill compliance models by allowing the simultaneous estimation of noncompliant and nonpersistent behaviors; the partitioning of their individual contributions to medication taking; and the appropriate estimation of noncompliance risk for patients with varying treatment persistence. The results from this model provide a more detailed description of the medication-taking process in addition to allowing a comparison of the differential influence of various risk factors on noncompliant and nonpersistent behaviors.

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