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METHODOLOGICAL ARTICLE

Dynamic Medication Adherence Modeling in Primary Prevention of Cardiovascular Disease: A Markov Microsimulation Methods Application

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ABSTRACT

Background: Real-world patients' medication adherence is lower than that of clinical trial patients. Hence, the effectiveness of medications in routine practice may differ. **Objectives:** The study objective was to compare the outcomes of an adherence-naive versus a dynamic adherence modeling framework using the case of statins for the primary prevention of cardiovascular (CV) disease. **Methods:** Statin adherence was categorized into three state-transition groups on the basis of an epidemiological cohort study. Yearly adherence transitions were incorporated into a Markov microsimulation using TreeAge software. Tracker variables were used to store adherence transitions, which were used to adjust probabilities of CV events over the patient's lifetime. Microsimulation loops "random walks" estimated the average accrued quality-adjusted life-years (QALYs) and CV events. For each 1,000-patient microsimulations, 10,000 outer loops were performed to reflect second-order uncertainty. **Results:** The adherence-naive model estimated 0.14 CV events avoided per person, whereas the dynamic adherence model estimated 0.08 CV events avoided per person. Using the adherence-naive model, we found that statin therapy resulted in 0.40 QALYs gained over the lifetime horizon on average per person while the dynamic adherence model estimated 0.22 incremental QALYs gained. Subgroup analysis revealed that maintaining high adherence in year 2 resulted in 0.23 incremental QALYs gained as compared with 0.16 incremental QALYs gained when adherence dropped to the lowest level. **Conclusions:** A dynamic adherence Markov microsimulation model reveals risk reduction and effectiveness that are lower than with an adherence-naive model, and reflective of real-world practice. Such a model may highlight the value of improving or maintaining good adherence.

Keywords: comparative effectiveness research, cost-effectiveness, decision-analytic model, medication adherence.

Introduction

Evidence used in drug evaluations is often based on results from randomized controlled trials (RCTs). It is known, however, that RCTs have limited generalizability to real-world populations due to their restrictive inclusion criteria [1,2]. One component of this limitation is patients' medication adherence. It is known that patients' medication adherence and persistence in the real world is often lower than that of trial patients [3]. This is especially true in the case of preventive medication for asymptomatic conditions such as statins for hyperlipidemia treatment in the setting of primary prevention for cardiovascular (CV) disease [4]. Decision-analytic models aiming to quantify the comparative or cost-effectiveness of drugs rarely take into account medication adherence and assume trial-based efficacy rather than real-world effectiveness [5]. Models typically assume a constant rate of medication adherence and impose the risk reduction rates from the trial onto the cohort in the simulated model. Such models are "naive" to potential transitions in adherence over time and related changes in drug effectiveness. This may be a limitation, particularly in a comparison between drug products whose trial-based efficacy may be similar but to which patients' adherence may be differential.

The ISPOR Economics of Medication Compliance and Persistence Working Group reviewed a number of methods that may be appropriate for incorporating adherence and persistence in cost-effectiveness analyses and cited studies that had incorporated such methods [6]. It was concluded that the inclusion of

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compliance and persistence in economic analyses was important, yet few studies have addressed it and therefore recommended that further research in this field is needed. Because decision makers increasingly desire real-world evidence for reimbursement decisions, research expands to address this need [7]. Methodology for simulation models used for both cost-effectiveness analysis and comparative effectiveness research should begin to address real-world medication adherence because it is linked to real-world effectiveness. Two previous statin modeling studies that have focused on adherence have illustrated that incorporating medication adherence is able to reveal the real-world cost-effectiveness of drugs [8,9]. There is still a need, however, for a simple and clear illustration of a practical modeling approach to which researchers may refer when tackling medication adherence simulation.

Two challenges exist in incorporating adherence patterns into a decision-analytic model. The first challenge is related to translating evidence about adherence and outcomes into model parameter estimation. The second is related to the Markov assumption: state transitions do not carry patients' history to the next state and therefore do not influence future transitions [10]. Although this may be overcome to some degree with the addition of states to reflect "postevent" consequences, the number of states needed to reflect this may quickly become unmanageable. We present a microsimulation modeling approach for overcoming these technical and conceptual challenges using an example of statins for the primary prevention of CV disease. Our objective was to incorporate real-world statin adherence estimates and related changes in drug effectiveness into a Markov microsimulation model to assess statins for primary prevention.

Methods

A published Markov cohort decision-analytic model was previously used to estimate the effectiveness of statin therapy as compared with no treatment for the primary prevention of CV events (myocardial infarction and stroke) in adults [11]. This model assumed static, RCT-comparable adherence and did not take into account medication adherence changes over time. We used this existing "adherence-naive" model as a foundation for a "dynamic adherence" model that incorporated real-world adherence transitions. The conversion of the adherence-naive model to a dynamic adherence model required both conceptual and technical additions to the model (Table 1). It was hypothesized that real-world adherence, known to be suboptimal, would lead to decreased effectiveness of statins, thereby preventing fewer CV events and reducing quality-adjusted life-years (QALYs) gained.

Model Structure and Assumptions

In the adherence-naive model, it was assumed that patients adhered to medications at a rate that achieved rates of efficacy observed in the RCT [12]. The model was naive to potential transitions in adherence over time. The model construction and simulation were performed using TreeAge Pro 2013 (TreeAge Software, Inc., Williamstown, MA).

Effectiveness, measured in QALYs, was estimated for each health state using community-based EuroQol five-dimensional questionnaire scores [13,14], which were accrued over 1-year cycle lengths until patients entered the absorbing state of death (CV-related or non-CV) or reached the age of 100 years. The model structure and parameters have been described at length in a previous publication [11]. Several adaptations were made to the published model and are described here. This reflected a primary prevention strategy for adults with average cholesterol levels, as seen in the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin [12]. The baseline rates of events (transformed into probabilities) and risk reduction associated with statins are described in Table 2. After experiencing an event in the model (e.g., nonfatal myocardial infarction or stroke), patients were assumed to experience the average costs, QALYs, and risk of death reflecting the cohort of individuals with existing CV disease in the United States (the postevent state, Fig. 1). The postevent state was a simplification of the reality that patients may experience multiple CV events, or develop heart failure. In addition, statin use was not explicitly modeled after patients experienced a CV event. The cohort's QALYs were calculated for the remainder of their lifetime on the basis of the average experience of the population that has survived a vascular event. One thousand model microsimulation loops "random walks" were performed to estimate the average accrued QALYs. For each group of microsimulations, second-order uncertainty was reflected by performing 10,000 outer loops. The chosen number of random walks and loops was deemed to be sufficiently large. In the outer loop, the following parameters were drawn from distributions representing the mean value: baseline probability of myocardial infarction and stroke, statin effectiveness, and statin effectiveness adjustment (where applicable) (Table 2). Subgroup analyses were performed to explore the changes in effectiveness for patients at each of the three adherence levels in their second year of statin use.

Conceptual Approach to Modeling Adherence

Medication adherence as a state-transition model

Statin adherence was conceptualized as "levels," to be more easily represented by a state-transition model. Adherence to statins measured on a continuous scale of proportion of days covered (PDC) was categorized into three levels similar to previous studies, as illustrated in Figure 1: PDC $\geq$ 0.80, 0.20 $\leq$ PDC $<$ 0.80, PDC $<$ 0.20 [15,16]. Adherence category (level) was assigned for each year, thereby allowing transition between levels after each yearly cycle.

Once adherence was conceptualized as a categorical measure, it was reflected as individual health states in a Markov state-transition model (Fig. 1). In the adherence-naive model, the "healthy" state represented patients who were taking statins and had not experienced a CV event. In the dynamic adherence model, the healthy state is illustrated as three individual healthy

Table 1 – Data needs for adherence-naive and dynamic adherence models

Model parameter	Adherence-naive model	Dynamic adherence model
Adherence transition probabilities	NA—In this model, it is assumed that patients maintain constant adherence at levels observed in the trial.	Estimates of the probability that patients will remain adherent to medication are used to inform transition probabilities.
Drug effectiveness	Risk reduction due to statins was based on RCT-reported efficacy for cardiovascular events of interest.	Evidence on the link between adherence transitions and changes in drug effectiveness are used to adjust RCT-based rates of efficacy.

NA, not applicable/available; RCT, randomized controlled trial.

Table 2 – Statin effectiveness adjustments associated with adherence.*

CV event	Baseline yearly probability†	Statin effectiveness† (risk ratio)	Adherence adjustment factor†,‡ (hazard ratio)		
	a	*b*	*c*	*c*	*c*
			PDC < .20	.20 ≤ PDC < .80	PDC ≥ .80
Myocardial infarction	0.0037 (β distribution α = 68, β = 8833)	0.46 SE: 0.102 (β distribution)	2.714 SE: 0.367 (γ distribution)	1.16 SE: 0.146 (γ distribution)	1
Stroke	0.0034 (β distribution α = 64, β = 8837)	0.52 SE: 0.115 (β distribution)			

CV, cardiovascular; PDC, proportion of days covered; SE, standard error.

* CV event probabilities were calculated as follows: Statin users: $a \times b \times c$. No statin: a only.

† These parameters were varied in 10,000 outer loops of the microsimulation to represent second-order uncertainty. The distribution type for each is described here.

‡ Ceiling limits were used such that the resulting CV risk could not be greater than the baseline risk.

states representing the three levels of adherence that may be exhibited by primary prevention statin users.

Data needs for the dynamic adherence model

To convert the adherence-naive model to the dynamic adherence model, a number of data needs were addressed with additional model parameter estimates relating to the conceptual addition of adherence to an existing Markov model. These data elements are summarized in Table 1 and explained in further detail below.

Adherence transition probabilities

The typical assumption of many models is that patients maintain trial-based adherence throughout model cycles. We modified this assumption by modeling patients beginning statin treatment with high adherence and modeling adherence transitions after the first year of treatment. These transition probabilities were informed by a published pharmacy claims analysis (Table 3) [17]. The yearly PDC was calculated by dividing the summed statin prescription fills by the number of days in the yearly time period. In each period, surplus statin from overlapping refills was carried forward and/or carried over to the following period, thereby reducing inflated adherence measures due to refills at the very end of the yearly period [18]. Because the interest of this study was patterns of statin exposure in primary prevention, adherence was estimated until the point of an identified CV event, or the end of 3 years. Transition probabilities were derived from these yearly adherence rates.

After the first year of statin use, individuals had a probability of remaining highly adherent, or transitioning to a lower level of adherence. Patients' year 2 adherence level was predictive of transition probabilities in year 3 and beyond. Adherence tended to decay over time, and patients had a higher probability of transitioning to lower levels such that few patients would remain in the highest level over time.

Drug effectiveness

Reduced medication adherence was assumed to result in reduced effectiveness, as evidenced in previous studies [19–22]. The magnitude of this effectiveness reduction was obtained from a previous study by the authors that estimated the association between changes in adherence to statins and changes in the risk of CV events (Table 2) [17]. The estimated association between the level of adherence and outcome was not linear and is described in detail below.

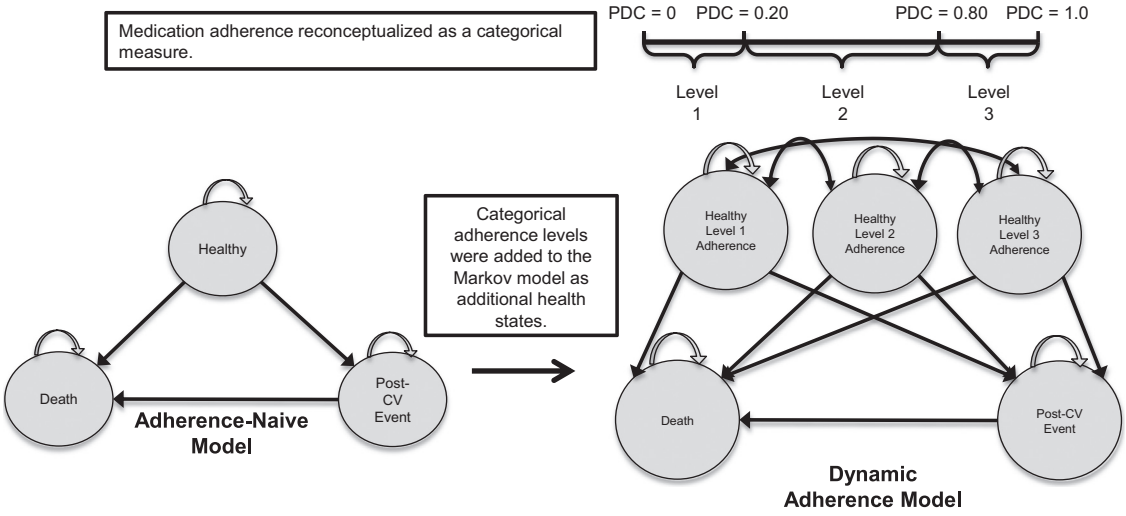

Fig. 1 – Conceptual conversion of adherence-naive to dynamic adherence model. CV, cardiovascular; PDC, proportion of days covered.

Table 3 – Adherence transition probabilities.

Year 1 adherence PDC ≥.80	Transition probabilities (year 3 and beyond)		
Transition probabilities (year 2)	PDC < .20	.20 ≤ PDC < .80	PDC ≥ .80
PDC < .20 6.08%	79.97%	11.99%	8.05%
.20 ≤ PDC < .80 23.70%	37.22%	34.27%	28.52%
PDC ≥ .80 70.22%	11.31%	15.77%	72.92%

PDC, proportion of days covered.

Technical Approach to Modeling Adherence

Technical conversion to the dynamic adherence model

The adherence-naive model was modified to a Markov microsimulation ("random walk") to incorporate patients' dynamic adherence. The model simulated the real-world scenario that a patient's adherence to statin therapy was variable according to observational data that are representative of the US census population and resulted in different outcomes [17]. It was assumed that individuals began statins exhibiting the highest level of adherence (≥80%), experienced trial-based statin effectiveness, and then experienced adherence transitions after the first cycle.

The adherence-naive model structure was modified to accommodate changing adherence levels (Fig. 2). This was accomplished by adding additional decision nodes at the end of the cycle. Individuals in the model who remained in the healthy state during the first cycle faced the probability of a transition in the adherence level at the end of the cycle, indicating the adherence level for the next model cycle (Fig. 2). As patients moved through the model, at the end of the year *i*, an initial transition probability informed the transition to an adherence level for the next year. Transition probabilities for subsequent cycles were selected given the adherence level in year *i* (Table 2). The level of adherence chosen at the end of year *i* was stored in a global matrix for year *i* +1 before the individual entered the next model year (*i* + 1) (Fig. 2). At the beginning of year *i* + 1, a tracker variable used the value stored in the global matrix to reflect the current cycle's adherence level. The selected level was also stored as a tracker variable for years 2 and 3, allowing post hoc subgroup analysis. This process continued for all model cycles in which the individual did not experience an event or death. The model was validated internally by comparing results of the naive- and dynamic adherence models. By using static adherence measures in the dynamic model, results similar to the naive model were produced.

Drug effectiveness changes

In the first cycle, patients' risk of CV and adverse events was unchanged because the highest level of adherence was assumed. In subsequent model cycles, these risks were adjusted given the level of adherence exhibited in that cycle. Results of a claims-based survival analysis were used to adjust the overall risk of events [17]. This study described increase in CV event hazard for changes in adherence after 1 and 2 years of statin use. Because of the lifetime horizon of this model, the hazard increases associated with adherence in the third year of statin use were applied

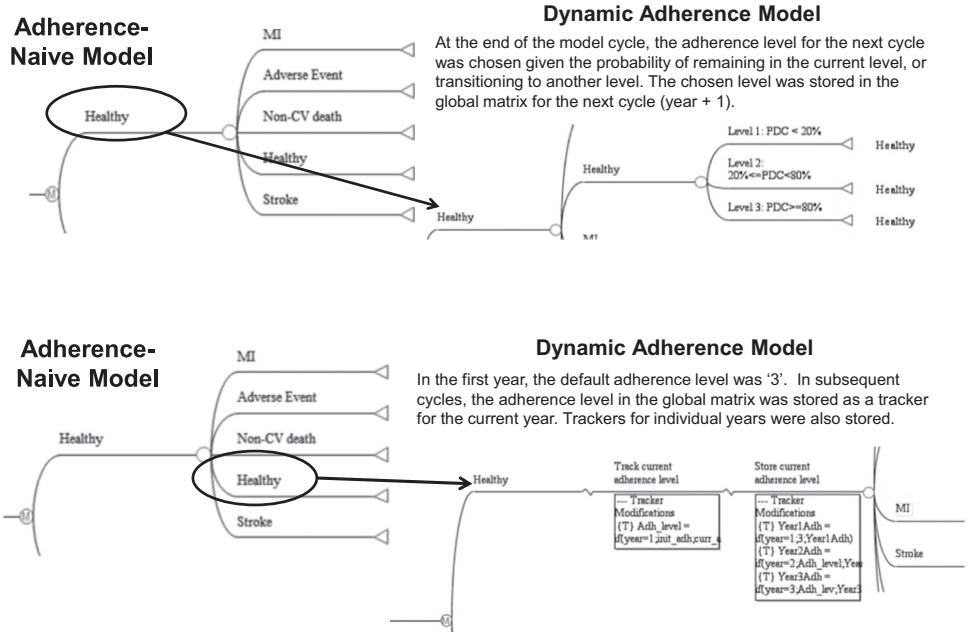

Fig. 2 – Technical conversion of adherence-naive to dynamic adherence model. CV, cardiovascular; MI, myocardial infarction; PDC, proportion of days covered.

to all model cycles. The risk changes are summarized in Table 2. Patients using statins had a baseline probability of CV events, which was multiplied by the trial-based rate of effectiveness (RCT risk ratio) [17]. The hazard ratios found in the aforementioned survival analysis (described in Table 2) then further adjusted the probabilities to reflect adherence behavior. Patients exhibiting the highest level of adherence were the reference group, such that their risk of CV events on statins was unchanged. Ceiling limits were used such that the resulting CV risk could not be greater than the baseline risk. The survival model results inform change in risk on the basis of two lags of adherence, years 2 and 3. The estimates for year 3 were used for all model cycles beyond year 3. Adverse event probabilities were assumed to be unchanged at all levels of adherence.

Results

In the dynamic adherence model simulated cohort, 69% of the patients exhibited highest adherence, 23% exhibited intermediate adherence, and 6% exhibited low adherence in year 2, and 2% experienced a CV event or died in the first year. Using the adherence-naive model (assumed static adherence seen in RCT), it was estimated that statin therapy resulted in 0.40 QALYs gained over the lifetime horizon on average per person. The dynamic adherence model estimated that statin therapy resulted in 0.22 incremental QALYs gained over the lifetime horizon on average per person. In the 10,000 trials simulated using 1000 patients in the adherence-naive model, statin therapy resulted in 0.14 CV events avoided per person. Using the dynamic adherence model, statin therapy resulted in 0.08 CV events avoided per person (Table 4). The difference in CV events by treatment group was statistically significant in both models. Subgroup analysis revealed that maintaining high adherence in year 2, followed by adherence transitions in subsequent years, resulted in 0.23 incremental QALYs gained and 0.08 events avoided as compared with 0.16 incremental QALYs gained and 0.07 events avoided when adherence dropped to the lowest level in year 2, followed by adherence transitions in subsequent years.

Discussion

This study provides a contribution to the modeling and comparative effectiveness literature by presenting a technical and conceptual framework for incorporating medication adherence into a Markov model. Although incorporating history into a Markov model is often unwieldy, recent work has shown its importance [23] and we have illustrated a straightforward approach for modeling adherence history. This work may serve as a practical guide for researchers wishing to build comparative effectiveness research models that incorporate real-world medication adherence evidence. Although the data needs for a dynamic adherence model may be viewed in the realm of parameter uncertainty, the choice to incorporate real-world adherence may be seen as an element of structural uncertainty. One may conceptualize dynamic adherence as a shift from one representative "healthy" state to several, as we have here. Because new ISPOR modeling guidelines have recently emerged [24], this approach may be considered by researchers wishing to

Table 4 – Markov microsimulation results

Overall analysis	QALYs gained, mean ± SD (95% CI)	Incremental QALYs gained	CV events, mean ± SD	CV events avoided with statin
Model type				
Adherence-naive model	Statin: 13.10 ± 0.16 (95% CI 12.78–13.41) No statin: 12.70 ± 0.15 (95% CI 12.40–13.00)	0.40	Statin: 0.18 ± 0.03 (95% CI 0.12–0.23) No statin: 0.32 ± 0.03 (95% CI 0.27–0.37)	0.14
Dynamic adherence model	Statin: 12.92 ± 0.19 (95% CI 12.55–13.29) No statin: 12.70 ± 0.15 (95% CI 12.40–12.99)	0.22	Statin: 0.24 ± 0.03 (95% CI 0.18–0.29) No statin: 0.32 ± 0.03 (95% CI 0.27–0.37)	0.08
Subgroup analysis: Dynamic adherence model	**QALYs gained, mean ± SD (95% CI)**	**Incremental QALYs gained**	**CV events, mean ± SD**	**CV events avoided with statin**
Adherence level in year 2*				
PDC < .20	Statin: 12.86 ± 0.19 (95% CI 12.48–13.23) No statin: 12.70 ± 0.15 (95% CI 12.40–12.99)	0.16	Statin: 0.25 ± 0.03 (95% CI 0.20–0.31) No statin: 0.32 ± 0.03 (95% CI 0.27–0.37)	0.07
.20 ≤ PDC < .80	Statin: 12.91 ± 0.19 (95% CI 12.54–13.28) No statin: 12.70 ± 0.15 (95% CI 12.40–12.99)	0.21	Statin: 0.24 ± 0.03 (95% CI 0.19–0.30) No statin: 0.32 ± 0.03 (95% CI 0.27–0.37)	0.08
PDC ≥ .80 (reference)	Statin: 12.93 ± 0.19 (95% CI 12.57–13.30) No statin: 12.70 ± 0.15 (95% CI 12.40–12.99)	0.23	Statin: 0.24 ± 0.03 (95% CI 0.18–0.29) No statin: 0.32 ± 0.03 (95% CI 0.27–0.37)	0.08

CI, confidence interval; CV, cardiovascular; PDC, proportion of days covered; QALY, quality-adjusted life-year.
* After year 2, patients' continued transitioning through adherence levels using the aforementioned transition matrix in Table 2.

address structural uncertainty in their modeling studies. Our modeling approach also provides a technical advantage over average patient cohort models by permitting simple subgroup analyses. The dynamic adherence model showed an overall difference in the QALYs gained and events avoided by subgroup. The Markov microsimulation approach allows the illustration of value differences by subgroup, an advantage over average patient cohorts. By examining the subgroup analysis results, we found that for those in the lowest level of adherence in year 2, although the least likely scenario, QALYs gained decrease and CV events increase than for those who remain at the highest level of adherence.

This study provides a platform for the comparison of drugs with differential adherence and a means to estimate the value of adherence-improving interventions. Although our example examined statin treatment versus no statin, this is simply an example to illustrate the approach. Statins are widely considered to be valuable and effective without question. This type of analysis, however, could be very useful in a case in which the relative effectiveness of a new drug is in question, and may have an advantage of better patient adherence. A model may use two active drug arms in which the adherence probability transition matrices vary (Table 3). Although good adherence to either drug may result in good clinical effectiveness, a priori evidence about patients' adherence may inform such a model and will provide both overall effectiveness results and subgroup results for low versus high adherers, such as in Table 4. This approach may be particularly useful to assess, for example, the new class of oral anticoagulants, in which adherence among the various agents may differ, and be compared to traditional strategies that incorporate closer patient monitoring. Recent literature has suggested that adherence be considered when selecting the appropriate anticoagulant for patients [25]. It will also be important to consider the value and effectiveness of agents given potential adherence [26]. In this case, a method for simulating patients' adherence will be valuable. This methodology may also be applied to a scenario in which severe adverse effects or undesirable dosing regimens greatly affect adherence and an alternative exists that does not pose such problems. Health care payers in the United States may be interested in such a methodology for these reasons.

A natural extension of this work is a cost-effectiveness model that incorporates medication adherence. Researchers may combine our approach of dynamic adherence modeling with recent research on modifying trial-based economic analyses to be reflective of clinical practice [27]. In the framework of a cost-effectiveness analysis, a subgroup analysis similar to ours in Table 4 may be used to interpret the value of an intervention that would help patients maintain high adherence [28,29]. This scenario may highlight the value of improving adherence, given the cost of doing so. This may be of particular interest in valuing the costs associated with interventions that improve adherence, a cited research priority [30,31]. From a payer perspective, such results may inform whether an intervention that ameliorates medication adherence is valuable to implement, given the lifetime costs associated with CV events, for example.

Our results may be compared with those of other studies that have modeled medication adherence [8,9]. Cherry et al. [8], in their study of adherence to antihypertensive drugs and statins, found that both real-world and trial-based adherence resulted in cost-effective strategies, but adherence similar to a trial was more cost-effective. Real-world adherence to both drugs resulted in an incremental cost-effectiveness ratio greater than the incremental cost-effectiveness ratio resulting from ideal adherence, such as that found in a trial. Their overall conclusion is similar to what is found in this study, despite their focus on cost-effectiveness. Mason et al. [9] incorporated statin adherence into a study to explore the optimal time to begin statin therapy in those with diabetes. They also found that as adherence increases to approach that seen in an RCT, statin therapy is more costly but more effective than low or intermediate adherence.

A number of limitations should be considered with the results of this study. The major assumption of our example is that of the effect of adherence transitions on outcomes. This may vary greatly by drug class or patient cohort, so it is important that researchers inform their dynamic adherence model parameters with appropriate evidence. Our input parameters for both adherence transitions and CV outcomes were derived from one sample of new statin users. Other studies have estimated some of these parameters, but none has estimated all parameters in the same cohort [16]. We chose to derive these using pharmacy claims, but researchers may consider evidence from RCTs or observational studies, while considering trade-offs typically associated with the hierarchy of research designs [32,33]. Such evidence could be used to validate a simulation model as well. Extensive model validation was not performed in this case. Future work should focus on validating simulated CV outcomes using real-world data. A typical assumption of models is that patients remain fully adherent to their medication for the duration of therapy. In this model, we modified that assumption and assumed that they were fully adherent the first year, but exhibit adherence transitions in subsequent years. Future studies may modify this assumption and attempt to characterize adherence in the first year. Given the nature of the parameter data available, it was desirable to focus on a homogeneous population for the survival analysis, but this should be further explored in future studies.

Conclusions

This study provides a novel approach for incorporating medication adherence into a model that may be used to assess the value of improving adherence or comparing outcomes among therapeutics with differential adherence. This study has two implications. First, we present an approach for modeling medication adherence: a methodological advancement that has been attempted by few thus far. Although this application of this modeling methodology is presented in a comparative effectiveness framework here, its applications may extend to cost-effectiveness analysis as well. Second, the post hoc analysis of such a model allows differences in effectiveness to be illustrated among adherence subgroups. In the interest of patient-centered research and personalized medicine, an approach that elucidates differences in patient subgroups increases the information gained over methods that use average patient cohorts.

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