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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.