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Development and Validation of Algorithms to Identify Statin Intolerance in a US Administrative Database

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ABSTRACT

Objectives: To develop and validate algorithms to define statin intolerance (SI) in an administrative database using electronic medical records (EMRs) as the reference comparison. **Methods:** One thousand adults with one or more qualifying changes in statin therapy and one or more previous diagnoses of hyperlipidemia, hypercholesterolemia, or mixed dyslipidemia were identified from the Henry Ford Health System administrative database. Data regarding statin utilization, comorbidities, and adverse effects were extracted from the administrative database and corresponding EMR. Patients were stratified by cardiovascular (CV) risk. SI was classified as absolute intolerance or titration intolerance on the basis of changes in statin utilization and/or the occurrence of adverse effects and laboratory testing for creatine kinase. Measures of concordance (Cohen's kappa [κ]) and accuracy (sensitivity, specificity, positive predictive value [PPV], and negative predictive value) were calculated for the administrative database algorithms. **Results:** Half of the sample population was white, 52.9% were women, mean age was 60.6 years, and 35.7% were at high CV risk. SI was identified in 11.5% and 14.0%, absolute intolerance in 2.2% and 3.1%, and titration intolerance in 9.7% and 11.8% of the patients in the EMR and the administrative database, respectively. The algorithm identifying any SI had substantial concordance ($\kappa = 0.66$) and good sensitivity (78.1%), but modest PPV (64.0%). The titration intolerance algorithm performed better ($\kappa = 0.74$; sensitivity 85.4%; PPV 70.1%) than the absolute intolerance algorithm ($\kappa = 0.40$; sensitivity 50%; PPV 35.5%) and performed best in the high CV-risk group (n = 353), with robust concordance ($\kappa = 0.73$) and good sensitivity (80.9%) and PPV (75.3%). **Conclusions:** Conservative but comprehensive algorithms are available to identify SI in administrative databases for application in real-world research. These are the first validated algorithms for use in administrative databases available to decision makers.

Keywords: administrative data, cardiovascular risk, claims data, electronic medical record, hypercholesterolemia, statin intolerance, validation.

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Introduction

Research has consistently demonstrated that statins decrease both the risk for cardiovascular (CV) events and mortality rates in patients with hypercholesterolemia [1,2]. Consequently, contemporary lipid management guidelines recommend statin therapy for patients with increased CV risk who are most likely to benefit in terms of atherosclerotic cardiovascular disease (ASCVD) risk reduction. The American College of Cardiology/American Heart Association guidelines identify four major statin benefit groups: 1) individuals with clinical ASCVD, 2) individuals with elevated low-density lipoprotein cholesterol (LDL-C; ≥190 mg/dl), 3) individuals with diabetes and increased LDL-C (70–189 mg/dl), and 4) individuals with estimated 10-year ASCVD risk of 7.5% or higher [3]. The National Lipid Association (NLA) recommends moderate- to high-intensity statin therapy for patients with ASCVD or diabetes mellitus, regardless of baseline lipid levels [4].

Despite the known benefits of statins, many patients, including those at high CV risk, discontinue treatment [5]. Experiencing statin-related adverse effects (AEs) is one of the most common reasons for statin switching or discontinuation [6]. Even among adherent patients, providers may not always be able to prescribe the preferred therapeutic dose as AE frequency increases with dose intensity [7,8]. The most common statin-associated AEs are muscle-related, and these have been documented in 16.0% to 32.9% of patients receiving statins and in 15.4% to 33.2% of

Conflicts of interest: At the time this work was completed, K. L. Schulman was a consultant for Sanofi US. L. E. Lamerato has received research support from Sanofi US. At the time this work was completed, M. R. Dalal was employed by and had ownership interest in Sanofi US. J. Sung, A. Koren, and U. G. Mallya are employed by and have ownership interest in Sanofi US. At the time this work was completed, M. Jhaveri was employed by Sanofi US. At the time this work was completed, J. M. Foody was a consultant for Merck, Pfizer, Bristol-Myers Squibb, Sanofi, and AstraZeneca.

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placebo-treated patients in long-term randomized clinical trials [9]. A number of other AEs, however, have been associated with statin therapy, including elevated transaminase, headache, insomnia, fatigue, dyspepsia, nausea, rash, alopecia, constipation, diarrhea, gastrointestinal disturbance, arthritis, and renal disorders [10–12]. Studies have estimated the incidence or prevalence of muscle-related symptoms (5%–25%), but these data are from clinical trials, single-site retrospective cohort studies, and patient surveys and as such may have limited generalizability to the larger population [6,13–18]. Factors associated with increased risk of statin intolerance (SI) include advanced age, clinical or subclinical hypothyroidism, and pre-existing liver or chronic kidney disease [19].

Although SI is recognized as a clinical entity, there is no consensus yet on a single definition [19,20], making it difficult to assess the incidence of SI. The Canadian Working Group (CWG) has defined SI as a clinical syndrome

> characterized by inability to use statins for long-term reduction of lipids and/or CV risk because of significant symptoms and/or biomarker abnormalities that can be temporally attributed to the initiation or dose escalation of statins; if appropriate, drug withdrawal and rechallenge can strengthen the association. [21(p1553)]

The NLA defines SI as

> a clinical syndrome characterized by the inability to tolerate at least 2 statins: one statin at the lowest starting daily dose AND another statin at any daily dose, due to either objectionable symptoms (real or perceived) or abnormal lab determinations, which are temporally related to statin treatment and reversible upon statin discontinuation, but reproducible by re-challenge, with other known determinants being excluded. [22(pS78)]

These definitions, although similar in many respects, differ in terms of mandating statin dosage and rechallenge and also with respect to the validity of patient symptoms.

Accurate identification of SI is important in terms of both establishing its incidence and characterizing the associated clinical, economic, and quality-of-life burdens, which are at present unknown. The objective of this study was to develop and validate algorithms to identify patients with SI in an administrative database on the basis of the overlap between CWG and NLA definitions.

Methods

Data Source

The data source selected to develop and validate the SI algorithms was from the Henry Ford Health System (HFHS). The HFHS offers primary, acute, and specialty care services in the Midwest and also includes a wholly owned nonprofit health maintenance organization, the Health Alliance Plan (HAP). HFHS data repositories include both an administrative database, which provides comprehensive medical billing and pharmacy claims data, and electronic medical records (EMRs), including laboratory results, from all sites of service, linkable for each patient using a lifetime patient identifier. This study was approved by the HFHS institutional review board.

Validation Study Sample

The validation study sample was drawn from the HFHS administrative claims database using the following criteria: adults (≥18 years) who 1) had one or more statin qualifying events between December 1, 2005, and November 30, 2010, 2) were continuously enrolled in HAP for 1 year before and 2 years after the qualifying event, and 3) had one or more diagnoses (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*]) of hyperlipidemia (272.4), hypercholesterolemia (272.0), or mixed hyperlipidemia (272.2) before the qualifying event (index) because lipid levels may have been influenced by existing statin therapy.

Qualifying events included statin discontinuation, switch, or a decrease in statin dosage. Statin switch events were eligible only if the patient switched from a high-intensity statin to a lower intensity statin or from a moderate/low-intensity statin to another moderate/low-intensity statin. Definitions of moderate/low-intensity and high-intensity statins were based on LDL-C–lowering capability. A statin was considered of high intensity or high potency if it reduced the LDL-C level from baseline by more than 45% (Table 1) [23,24].

If a patient had multiple qualifying events, the first qualifying event that met the eligibility criteria was selected. If the statin medication pattern for an individual patient met the criteria for both moderate/low-intensity and high-intensity statins, only the high-intensity qualifier was selected, although this did not exclude evaluation of the low-intensity statin if it also occurred during the study observation window. Study index was the date of each qualifying event. All patients were observed for 1 year pre- and 2 years postindex.

A sample of 1000 patients was drawn from the pool of eligible patients. Patients were categorized as being at high CV risk if they had two or more *ICD-9-CM* diagnoses of diabetes, coronary heart disease, or peripheral artery disease in the 12 months before the qualifying event on outpatient claims on different days or a single diagnosis on an inpatient claim. Data on patients' demographic and clinical characteristics, statin utilization, and AEs were extracted electronically from the administrative database. Statin utilization and AEs data were simultaneously abstracted from the EMR by three trained and credentialed research associates, after completion of a pilot study. Patients with unresolvable conflicts in the EMR or data quality issues in pharmacy claims were excluded from the study.

Statin Utilization and AEs

Statin exposure windows were created to characterize statin utilization and to identify associated AEs. Exposure windows were created independently on the basis of the statin regimen (statin plus dose) prescribed in the EMR as well as on statin fill records from pharmacy data in the administrative database. If present during an exposure window, SI was identified and confirmed.

The following information was abstracted from the EMR: statin prescription dates and dosage, AE type and date, whether changes in prescription were linked to an AE, and the primary and secondary reasons for statin discontinuation or dose lowering, if applicable. A prescription was end-dated if there was an absence of documentation for more than 12 months. Prescription records were then collapsed if the statin name and dosage were unchanged.

Statin exposure windows based on the administrative data relied on pharmacy claims. Periods of continuous use for each statin regimen were identified, allowing for a 30-day gap in the daily drug coverage pattern. In addition, a 45-day grace period was appended to the end of the exposure window for each statin regimen to account for verbal changes in physician instruction that were not reflected in the pharmacy claims records.

A list of AEs (primary and secondary) related to statin use was compiled (Table 2) [10–12]. The occurrence of an AE was based on the documentation of either the clinical term or the *ICD-9-CM* diagnosis code for an eligible AE in the EMR and independently based solely on the documentation of an *ICD-9-CM* diagnosis code for one of the eligible AEs in administrative data.

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