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Original Contribution

Clinical and economic consequences of statin intolerance in the United States: Results from an integrated health system

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BACKGROUND: Although statins are considered safe and effective, they have been associated with statin intolerance (SI) in clinical and observational studies.

OBJECTIVE: The objective of this study was to describe the clinical and economic consequences of SI through comparison of an SI cohort of patients with matched controls.

METHODS: This study used data extracted from an integrated health system's electronic health records from 2008 to 2014. Adults with SI were matched to controls using a propensity score. Patients were hierarchically classified into 6 mutually exclusive cardiovascular (CV)-risk categories: recent acute coronary syndrome (ACS; ≤12 months preindex), coronary heart disease, ischemic stroke, peripheral artery disease, diabetes, or primary prevention. The study endpoints, low-density lipoprotein cholesterol (LDL-C) goal attainment, medical costs, and time to first CV event were compared using conditional logistic regression, generalized linear, and Cox proportional hazards models, respectively.

RESULTS: Patients with SI (n = 5190) were matched with controls (n = 15,570). Patients with SI incurred higher medical costs and were less likely to reach LDL-C goals than controls. Patients with SI were at higher risk for revascularization procedures in all CV risk categories except ACS, and those in the diabetes risk category were at higher risk for any CV event. There was a lower risk of all-cause death among patients with SI.

CONCLUSIONS: Patients with SI were less likely to reach LDL-C goals, incurred higher health care costs, and experienced a higher risk for nonfatal CV events than patients without SI. Alternative management strategies are needed to better treat high CV risk patients.

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Introduction

Given the evidence in support of statins for reducing low-density lipoprotein cholesterol (LDL-C) and atherosclerotic cardiovascular disease events,[1–4] statins are the lipid-modifying therapy (LMT) that is most widely recommended by cholesterol management guidelines.[5–9] Despite

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these recommendations, data suggest that statins are underutilized even among patients with established atherosclerotic cardiovascular disease.[10–13] One cause for underutilization, suboptimal dosing, adherence, and discontinuation is statin intolerance (SI) resulting mainly from muscle-related symptoms.[7,14,15] The real-world prevalence of SI due to muscle-related symptoms has been reported to be as high as 25%.[7,16–22]

Currently, there is no gold-standard definition of SI, although guidelines and major organizations have attempted to clarify the definition.[7,15,23,24] The National Lipid Association (NLA) SI Panel (a component of the Statin Safety Assessment Task Force) defines SI as a decision to decrease or stop the use of an otherwise beneficial statin because of adverse effects, which can most often be attributed to muscle-related symptoms impacting quality of life.[15,25] Specifically, the NLA characterizes SI as a clinical syndrome defined by the inability to tolerate ≥2 statins as a result of unwanted symptoms (real or perceived) or abnormal laboratory values: one statin at the lowest starting daily dose and another at any daily dose. Other known causes of these symptoms should be excluded, and symptoms should be temporally related to statin treatment, reversible on discontinuation, and reproducible by reexposure. The NLA definition is consistent with definitions and guidance from other groups, including the European Atherosclerosis Society Consensus Panel and the Canadian Consensus Working Group.[7,26] Many guidelines and recommendations advocate maintaining therapy even in patients with SI because of the clinical benefits associated with statins.[7,8,27,28]

Despite the reported prevalence of SI,[7,16–22] the clinical and economic impacts of SI are largely unknown. Therefore, the objectives of this study were to summarize the clinical characteristics of patients with SI and to quantify differences in LDL-C goal attainment, health care costs, and CV events among patients with SI compared with a matched cohort of statin users who do not have SI.

Materials and methods

Study design and environment

This retrospective observational study extracted data from the Geisinger Health System (GHS) electronic health record (EHR) from January 1, 2008, through September 30, 2014. This study was approved by the Geisinger Institutional Review Board.

Patient population and subgroups

Patients ≥18 years and who had ≥12 months of health system encounters during the study period were included. Patients with a history of SI were identified by either a GHS custom diagnosis code (EP914) or *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)*[29] 995.27 (other drug allergy) code, with the specific statin medication added to the patient's allergy list. The date of SI diagnosis was considered the patient's index date. Eligible control patients were identified as being prescribed a statin but did not have a recorded diagnosis of SI. One encounter per patient (occurring ≥6 months after his/her first encounter and ≥6 months before his/her last encounter) was randomly selected to be the control patient's index date. Patients were excluded if they were diagnosed with cancer, human immunodeficiency virus, AIDS, or end-stage renal disease as defined by *ICD-9-CM*[29] diagnosis codes; had chronic kidney disease requiring dialysis as defined by Current Procedural Terminology (CPT) procedure codes; were in hospice or nursing home care, or required hospitalization with a length of stay >30 days before the index date. The LMT at index date was recorded for each patient. High-intensity statin therapy was defined by the prescribed strength: atorvastatin (40 or 80 mg), rosuvastatin (20 or 40 mg), or simvastatin 80 mg. Moderate-intensity to low-intensity statin therapy was defined as all other statin dosage forms.

Eligible patients were hierarchically classified into 6 mutually exclusive CV-risk categories (categories 1–5 were defined as high CV-risk conditions) based on the presence or absence of the foremost risk factors with the following organizational scheme: (1) inpatient hospitalization for myocardial infarction (MI) or unstable angina (UA) ≤12 months before the index date (recent acute coronary syndrome [ACS]); (2) history of old MI, stable angina, coronary revascularization procedure or chronic ischemic heart disease, or acute MI or UA >12 months before the index date (coronary heart disease [CHD]); (3) history of ischemic stroke; (4) history of peripheral artery disease (PAD); (5) history of diabetes (type 1 or type 2); or (6) primary prevention patients (defined as patients with none of the high CV-risk conditions 1–5). All CV risk conditions were identified during the preindex period by *ICD-9-CM* diagnosis codes and *ICD-9-CM*, CPT, and Healthcare Common Procedure Coding System procedure codes. Codes felt to represent conditions or events for which statins might not be indicated (eg, ischemic stroke in a participant with atrial fibrillation or valvular disease) were excluded. A complete list of diagnosis and procedure codes is provided (Supplemental Table 1).

To minimize potential confounding and selection bias between the 2 groups, patients with identified SI were matched to control patients using propensity score matching (PSM). The probability of SI was estimated by fitting a logistic regression model with the following covariates: age, sex; Charlson comorbidity index; CV-risk category; renal disease; active prescription for angiotensin-converting enzyme inhibitor; active prescription for angiotensin receptor blocker; active prescription for beta blockers; any medical costs in the prior 12 months; and total medical costs in the prior 12 months. Propensity scores were assigned to each patient in the population, and then a