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Clinical and economic outcomes in a real-world population of patients with elevated triglyceride levels

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ABSTRACT

Objective: This study investigated real-world treatment patterns, healthcare utilization, and costs of hypertriglyceridemia in a large commercially insured United States population. **Methods**: This observational claims study was conducted among adult patients with TG > 500 mg/dL between 01/01/2007 and 04/30/2013. Patients were stratified into mutually exclusive cohorts based on their first available TG measurement (index date): TG ≥ 1500 (Cohort A); 750 ≤ TG < 1500 (Cohort B), and 500 < TG < 750 (Cohort C). Study inclusion required ≥12 months of eligibility pre- (baseline) and post–index date (follow-up). Patient characteristics and outcomes were assessed descriptively. Costs associated with acute pancreatitis episodes were estimated using a Generalized Linear Model regression. **Results**: We identified a total of 1964 patients in Cohort A, 7432 in Cohort B, and 17,500 in Cohort C. Patients were young (mean age 46–48) and mostly male (75%–80%). Treatment switching and augmentation occurred rarely, and almost 50% of patients discontinued their initial treatment. At baseline, healthcare utilization and costs were highest in Cohort A (mean all-cause medical and pharmacy costs, $8850). At follow-up, the number of patients with dyslipidemia-related office and pharmacy claims and related costs almost doubled across the cohorts. Mean all-cause costs/patient in Cohort A at follow-up were $12,642, of which $3730 were dyslipidemia-related. Acute pancreatitis episodes were associated with >300% increase in total all-cause costs in Cohort A. **Conclusions**: These results suggest that severe hypertriglyceridemia is undertreated and healthcare utilization and costs scale with magnitude of TG elevation. Patients with more severe hypertriglyceridemia received greater medical and pharmacy services. Managing severe hypertriglyceridemia more aggressively and preventing acute pancreatitis may generate cost savings.

1. Introduction

Hypertriglyceridemia (HTG) is prevalent among a third of the adult population in the United States (US) [17]. HTG is defined as fasting blood plasma triglyceride (TG) levels ≥150 mg/dL by the National Cholesterol Education Program Adult Treatment Panel III [15,16]. The prevalence of severe HTG (TG > 500 mg/dL) is approximately 2% among adult Americans [27].

HTG is a defining feature of the metabolic syndrome and is commonly encountered in patients with diabetes mellitus (DM) and chronic kidney disease [22]. Severe HTG is multifactorial and a large number of genetic polymorphisms are etiologic for this metabolic phenotype. Chylomicronemia (type I dyslipoproteinemia), familial hypertriglyceridemia (type IV dyslipoproteinemia), and familial mixed hypertriglyceridemia (type V dyslipoproteinemia) arise from derangements in the metabolism of chylomicrons, very low-density lipoproteins (VLDL), or a combination of chylomicrons and VLDL, respectively [7,14].

Some studies suggest that HTG is associated with increased risk for coronary heart disease and its complications [2,21]. In the

Abbreviations: CVD, cardiovascular disease; HTG, hypertriglyceridemia; OR, odds ratio; TG, triglyceride.

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setting of severe HTG, serum concentrations of remnant lipoproteins (incompletely digested chylomicrons and VLDLs) are dramatically increased. Recent analyses from prospective epidemiologic cohorts strongly suggest that lipoprotein remnants are atherogenic [10,13,24] and are associated with increased risk of stroke [9] and coronary events [23]. One of the most clinically important complications of severe HTG is acute pancreatitis, an extremely painful and life-threatening condition that increases risk for chronic epigastric pain, DM, and pancreatic digestive enzyme deficiency [3,12,25,26]. Approximately 10% of cases of acute pancreatitis and 56% of cases of gestational pancreatitis occur in patients with severe HTG [1]. Other complications associated with severe HTG include lipemia retinalis, sensory neuropathy, chronic abdominal pain, tubero-eruptive xanthomas, and hepatosplenomegaly.

Treatment approaches for the management of severe HTG include aggressive restriction of dietary saturated fat intake, enriching the diet with medium chain fatty acid, relieving insulin resistance which may be contributory (weight loss, exercise, and smoking cessation), and the use of such drugs as statins, fibrates, niacin, and omega-3 fish oils [8,11,15,16,19,28]. The fibrates and fish oils can be especially helpful since they not only reduce hepatic VLDL production and secretion, but also activate lipoprotein lipase. However, challenges remain in identifying individuals at high risk for development of severe HTG complications, especially acute pancreatitis [5].

Currently, real-world data on the clinical and demographic characteristics, healthcare utilization patterns and costs associated with severe HTG are limited, and as a result this group of patients is inadequately characterized. The goal of this retrospective claims study was to examine the treatment patterns, clinical outcomes, healthcare utilization, and costs associated with severe HTG. In addition, we examined the incidence and costs associated with acute pancreatitis episodes.

2. Methods

2.1. Study design and population

The data for this retrospective cohort study consisted of medical and pharmacy administrative claims and electronic laboratory results taken from the HealthCore Integrated Research Database (HIRD^{SM}) for the period 01/01/2006 through 04/30/2013. The HIRD is a repository of longitudinal claims data from 14 geographically dispersed US commercial health plans with approximately 36 million lives. Patients with severe HTG – defined as TG > 500 mg/dL for the purposes of this study – between 01/01/2007 and 04/30/2012 were stratified into three mutually exclusive cohorts based on their first available TG measurement (index date): Cohort A (TG $\geq$ 1500); Cohort B (750 $\leq$ TG < 1500) and Cohort C (500 < TG < 750 mg/dL). The index therapy for each included patient was determined as the closest relevant pharmacy fill (for fish oil, fibrates, niacin, statins or other lipid lowering agents) relative to the index date, within an allowable time period between the index date (inclusive) and index date +120 days. Index therapy was set to missing when no relevant pharmacy fills were observed.

In this non-experimental study, all materials were handled in strict compliance with the Health Insurance Portability and Accountability Act (HIPAA). Data were kept anonymous throughout and patient confidentially was safeguarded; researchers only accessed a limited data set devoid of any individual patient identifiers. The study was performed under the Research Exception provisions of the Privacy Rule, 45 CFR 164.514(e), which exempted it from Investigational Review Board (IRB) approval.

2.2. Inclusion/exclusion criteria

To be included in the study, patients were required to be at least 18 years of age and to have at least one result for an electronic laboratory claim with an elevated triglyceride level of at least 500 mg/dL. Inclusion also required $\geq$12 months (360 days) continuous medical and pharmacy enrollment before the index date (baseline period) and $\geq$12 months (360 days) continuous medical and pharmacy enrollment (follow-up period) after the index therapy fill (or after index date if no index therapy fill was observed). Patients who had at least one claim for pregnancy during the baseline or follow-up period were excluded as pregnancy could temporarily increase TG levels. This study did not include any patients receiving Medicare coverage.

2.3. Patient characteristics and outcome measures

2.3.1. Baseline only

Patient characteristics including age, gender, geographic location and comorbidities were evaluated for the baseline period. Mean baseline comorbidity scores were measured with the Quan-Charlson comorbidity index [20].

2.3.2. Baseline and follow-up

Treatment patterns and the prevalence of conditions associated with ICD-9-CM code 272.xx were assessed during the pre- and post–index periods. Medication utilization was evaluated around index date (index date ±30 days) and again at 6-month follow-up (index date +150 days to index date + 210 days). Physician specialty was assessed at the time of the index therapy fill and during follow-up. In a subgroup of TG-treatment naïve patients, we evaluated treatment discontinuation, switching, and augmentation, as well as medication adherence using Proportion of Days Covered (PDC). PDC was measured as the proportion of the sum of the number of non-overlapping days with the index drug on-hand divided by the number of days in the follow-up period.

Laboratory test results were assessed around index date and 12 months follow-up for TG levels, low density lipoprotein cholesterol, high density lipoprotein cholesterol, total cholesterol, and HbA1c.

All-cause and disease-related healthcare resource utilization and costs were evaluated both at baseline and during follow-up. Disease-related utilization included all medical claims with an ICD-9-CM code for dyslipidemia (272.xx) and all pharmacy claims for TG-related medications including fibrates, fish oils, and niacin. Pancreatitis-related health care resource utilization and costs included all medical claims with an ICD-9-CM code of 577.0x and all pharmacy claims for digestive enzymes. Costs were computed as the total of plan paid plus patient paid amounts, and presented at constant 2013 US dollars. All utilization and cost measures were stratified by place of service (inpatient hospitalizations, standalone emergency room visits, physician office visits, and other outpatient visits).

2.4. Statistical analysis

Descriptive analyses included means (standard deviations [SD]) and relative frequencies for continuous and categorical variables, respectively. No comparisons were made across cohorts defined by TG levels. Within Cohort A, subgroups defined by the presence or absence of acute pancreatitis at follow-up were compared with two-sample *t*-tests or non-parametric tests as appropriate for continuous variables, and with chi-square tests or Fisher's exact tests for categorical variables.

A multivariable logistic regression was performed on Cohort A using acute pancreatitis over follow-up as the outcome and TG level