CLINICAL RESEARCH STUDY

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# Determining Triglyceride Reductions Needed for Clinical Impact in Severe Hypertriglyceridemia

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## ABSTRACT

**BACKGROUND:** Patients with severe hypertriglyceridemia have an increased risk of cardiovascular disease and pancreatitis. Target triglyceride levels associated with clinical benefit for patients with severe hypertriglyceridemia are not currently known. This study evaluates the association between lower follow-up triglyceride levels and incidence of clinical events for patients with severe hypertriglyceridemia.

**METHODS:** By using claims data from 2 large US healthcare databases, we conducted a retrospective cohort study and identified 41,210 adults with severe hypertriglyceridemia (triglycerides ≥500 mg/dL) between June 2001 and September 2010. The date of the first severe hypertriglyceridemia laboratory result was the index date. Patients were categorized into 1 of 5 triglyceride ranges (<200 mg/dL, 200-299 mg/dL, 300-399 mg/dL, 400-499 mg/dL, and ≥500 mg/dL) based on a follow-up triglyceride level assessed 6 to 24 weeks after initial triglyceride levels were measured. Adjusted Cox regression models were developed to evaluate the impact of follow-up triglyceride levels on rates of pancreatitis episodes and cardiovascular events.

**RESULTS:** The mean age of patients was 50 years, 72% were male, and the mean follow-up was 825 days. Patients with severe hypertriglyceridemia with follow-up triglyceride levels <200 mg/dL experienced a lower rate of pancreatitis episodes (adjusted incidence rate ratio, 0.45; 95% confidence interval, 0.34-0.60) and cardiovascular events (adjusted incidence rate ratio, 0.71; 95% confidence interval, 0.64-0.78) with some clinical benefit in adults with severe hypertriglyceridemia with follow-up triglyceride levels 200 to 299 mg/dL and 300 to 399 mg/dL ($P < .001$ for trend).

**CONCLUSIONS:** We observed the greatest impact on clinical events among patients with severe hypertriglyceridemia with the lowest follow-up triglyceride levels.

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**KEYWORDS:** Cardiovascular; Epidemiology; Pancreatitis; Severe hypertriglyceridemia

There are approximately 3 to 4 million adults in the United States with severe hypertriglyceridemia, defined as having triglyceride levels ≥500 mg/dL.[1] Triglyceride levels ≥150 mg/dL are associated with an increased risk of cardiovascular disease in men and women.[2] Severe hypertriglyceridemia is associated with an even greater risk of acute pancreatitis,[3] premature coronary heart disease,[4,5] and mortality due to cardiovascular disease.[6] Some of the risk factors associated with severe hypertriglyceridemia include genetic disorders, lifestyle factors (eg, excess alcohol intake, cigarette smoking, physical inactivity, and high carbohydrate diets), certain drugs (eg, hormone therapy), and other diseases (eg, type 2 diabetes, chronic renal failure, and metabolic syndrome).[7]

The current guidelines from the National Cholesterol Education Program Adult Treatment Panel III[7] recommend reducing triglycerides to less than 500 mg/dL to prevent acute pancreatitis before addressing issues related to

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**Authorship:** All authors had access to the data and played a role in writing this manuscript.

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non−high-density lipoprotein cholesterol and low-density lipoprotein cholesterol for patients with severe hypertriglyceridemia. Indeed, one study[8] found that 20% of patients with severe hypertriglyceridemia experience at least 1 episode of acute pancreatitis, the majority of which were considered severe. Therefore, the primary clinical recommendations for patients with severe hypertriglyceridemia are to decrease triglycerides to first reduce the risk of acute pancreatitis, with a secondary focus on decreasing cardiovascular risk. Guideline recommendations for reducing triglycerides include the use of triglyceride-lowering treatments (eg, fibrates, niacin, and omega-3 fatty acids), in addition to lifestyle modification (eg, weight control and increased physical activity).

Although lowering triglyceride levels is recommended to reduce the risk of coronary heart disease and cardiovascular events,[9] there is little evidence to demonstrate the impact of triglyceride reductions on the risk of clinical events in patients with severe hypertriglyceridemia.[10-12] In addition, among patients with severe hypertriglyceridemia, the level of triglyceride reduction that is associated with a reduced risk is not currently known. The primary objective of this study was to examine the association between the follow-up triglyceride levels and the incidence of pancreatitis episodes and cardiovascular events among patients with severe hypertriglyceridemia.

**CLINICAL SIGNIFICANCE**

- Although target triglyceride levels associated with clinical benefit for patients with severe hypertriglyceridemia (≥500 mg/dL) currently are not known, our study showed that patients with severe hypertriglyceridemia who decreased their triglyceride levels to <200 mg/dL experienced the greatest benefit.
- Patients with triglycerides of <200 mg/dL at follow-up had lower rates of pancreatitis and cardiovascular events, such as acute myocardial infarction, ischemic stroke, heart failure, revascularization procedures, and acute coronary syndrome.
- The results reflect real-world, objective clinical data from a large geographically diverse patient population over 2 years.

## MATERIALS AND METHODS

### Data Sources

This was a retrospective cohort study using medical, pharmacy, laboratory, and enrollment claims information from 2 large, US health care claims databases (Optum's Research Database; IMPACT National Benchmarking Database [formerly known as IHCIS]). Individuals covered by these health plans have medical and pharmacy benefits through commercial or Medicare Advantage insurance and are geographically diverse across the United States. Medical (professional, facility) claims included International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis codes, ICD-9 procedure codes, Current Procedural Terminology, Version 4 procedure codes, Healthcare Common Procedure Coding System procedure codes, and site of service codes. Outpatient pharmacy claims provided National Drug Codes for dispensed medications, quantity dispensed, drug strength, and number of days of supply.

All study data were accessed using techniques compliant with the Health Insurance Portability and Accountability Act of 1996,[13] and no identifiable protected health information was extracted during the course of the study. Because this study involved analysis of preexisting, de-identified data, institutional review board approval was not required.

### Study Patient Identification

We identified 104,817 adult patients who had at least 1 triglyceride laboratory result ≥500 mg/dL during the study period between June 1, 2001, and September 30, 2010; had continuous enrollment with medical and pharmacy claims for 6 months before the index date and at least 90 days after the index date; and had no medical claims indicating pregnancy. The index date was the date of the first severe hypertriglyceridemia laboratory result during the study period. We then limited our sample to the 41,210 patients who had at least 1 follow-up triglyceride laboratory result during a period of 6 to 24 weeks after the index date. The date of the earliest triglyceride laboratory result in this period was set as the *follow-up laboratory date*. Patients were then categorized into 1 of 5 follow-up triglyceride level ranges on the basis of their follow-up triglyceride laboratory result (<200 mg/dL, 200-299 mg/dL, 300-399 mg/dL, 400-499 mg/dL, and ≥500 mg/dL).

### Study Measures

**Patient Demographics and Baseline Clinical Characteristics.** The patient characteristics that were examined included age, gender, insurance type, geographic location, and length of the follow-up period (days). The baseline clinical characteristics that were collected during the 6 months preceding the index date included the Quan-Charlson comorbidity score,[14] history of cardiovascular disease, hypertension, dyslipidemia, diabetes mellitus, pancreatitis, chronic kidney disease, end-stage renal disease, and medication use (statins, triglyceride-lowering agents, hormone replacement therapy, steroids, and beta-blockers). The use of statins and triglyceride-lowering medications also was evaluated during the period between the index triglyceride result and the follow-up triglyceride result. Also examined were baseline triglycerides, total cholesterol, high-density lipoprotein, and non−high-density lipoprotein values.