Title

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Journal

Cardiology and Therapy, 9(1)

ISSN

2193-8261

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Publication Date

2020-06-01

DOI

10.1007/s40119-020-00170-x

Peer reviewed

Cardiol Ther (2020) 9:207–213
https://doi.org/10.1007/s40119-020-00170-x

BRIEF REPORT

Prevalence of US Adults with Triglycerides ≥ 150 mg/dl: NHANES 2007–2014

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Received: March 17, 2020 / Published online: April 23, 2020

ABSTRACT

Introduction: Hypertriglyceridemia is associated with increased atherosclerotic cardiovascular disease (ASCVD) event risk, which persists even in statin-treated patients. The objective of this analysis was to estimate the prevalence of triglyceride (TG) levels ≥ 150 mg/dl in statin-treated adults with diabetes or ASCVD in the United States.

Methods: Laboratory data, medical history, and prescription data from 40,617 subjects who participated in the US National Health and Nutrition Examination Survey (NHANES) spanning 8 years (four 2-year surveys; 2007–2014) were analyzed. Patients included were ≥ 20 years old and had morning fasting (at least 8.5 h) TG values available. The proportion and weighted number of individuals in the US population with TG ≥ 150 mg/dl was calculated according to statin use, as well as in key subgroups of statin-treated patients including those with low-density lipoprotein cholesterol (LDL-C) levels < 100 mg/dl, type 2 diabetes, ASCVD, and those with type 2 diabetes and ASCVD.

Results: A total of 9593 subjects, projected to represent 219.9 million Americans, met the study entry criteria and were included in the analysis. Of these, 2523 had TG levels ≥ 150 mg/dl, translating to a prevalence of 25.9% and representing 56.9 million Americans. Among statin-treated adults, the proportion with TG levels ≥ 150 mg/dl was 31.6% (12.3 million) and ranged from 27.6 to 39.5% for those who also had LDL-C levels < 100 mg/dl and type 2 diabetes or ASCVD.

Conclusions: Over 12 million Americans are treated with a statin and have TG levels ≥ 150 mg/dl. Interventions such as icosapent ethyl that have been shown to reduce ASCVD event risk in this elevated TG population with type 2 diabetes or established ASCVD can provide substantial clinical benefit for these patients.

Keywords: ASCVD; Cardiovascular disease; Eicosapentaenoic acid; Hypertriglyceridemia; Icosapent ethyl

Digital Features To view digital features for this article go to https://doi.org/10.6084/m9.figshare.12123921.

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Key Summary Points

Why carry out this study?

Hypertriglyceridemia is an important risk factor for atherosclerotic cardiovascular disease (ASCVD) events, even in statin-treated patients.

This study attempted to estimate the prevalence of hypertriglyceridemia in statin-treated patients in the United States, including those with type 2 diabetes or ASCVD.

What was learned from this study?

The overall prevalence of statin-treated patients with triglyceride levels ≥ 150 mg/dl in the United States is 25.9%.

A total of 12.3 million statin-treated patients have triglyceride levels ≥ 150 mg/dl, including as many as 6.4 million with type 2 diabetes or ASCVD.

INTRODUCTION

Hypertriglyceridemia is associated with increased atherosclerotic cardiovascular disease (ASCVD) event risk [1–4], and is highly prevalent in adults in the US due to genetic polymorphisms in triglyceride (TG) metabolism and to the increasing prevalence of obesity, insulin resistance, and diabetes mellitus. Guidelines suggest that target TG levels should be < 150 mg/dl for reduced ASCVD event risk [5]. The American Heart Association suggests that a TG level < 100 mg/dl may be optimal [6]. Elevated ASCVD event risk associated with elevated TG levels persists even in statin-treated patients; in the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) study, which evaluated atorvastatin and pravastatin, on-treatment TG levels of < 150 mg/dl versus ≥ 150 mg/dl were more predictive of a lower coronary heart disease risk than low-density lipoprotein cholesterol (LDL-C) levels of < 70 mg/dl versus ≥ 70 mg/dl [7]. Recent claims-based database analyses have attempted to quantify the cardiovascular event risk associated with elevated TG levels. In an analysis of the Optum Research Database, patients with TG levels ≥ 150 mg/dl were significantly more likely to have an initial major cardiovascular event than a corresponding propensity-matched cohort with TG levels < 150 mg/dl (hazard ratio [HR] 1.26; 95% confidence interval [CI] 1.19–1.34; $P < 0.001$) [8]. These analyses also indicated that elevated TG levels (i.e., ≥ 150 mg/dl) significantly predicted new heart failure diagnosis and hospitalization for new-onset kidney disease [9, 10]. The direct healthcare costs associated with TG levels ≥ 150 mg/dl were also significantly increased compared to costs for patients with more desirable TG levels (< 150 mg/dl), with an incremental cost burden across the US of $10.7 billion in statin-treated patients with hypertriglyceridemia [11].

The recent Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial (REDUCE-IT) demonstrated that the purified and stable eicosapentaenoic acid (EPA) formulation icosapent ethyl significantly reduced the risk of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina compared with placebo in high-risk, statin-treated patients with TG levels ≥ 150 mg/dl, established cardiovascular disease or diabetes, and well-controlled LDL-C (< 100 mg/dl) (HR 0.75; 95% CI 0.68–0.83; $P < 0.001$) [12]. As a result, the indication for icosapent ethyl has recently been expanded to include its use as an adjunct to maximally tolerated statin therapy (defined as the highest tolerated intensity and frequency of a statin, even if the dose is zero) for reduction of cardiovascular events among adults with TG levels ≥ 150 mg/dl and either established cardiovascular disease or diabetes mellitus and at least two additional risk factors for ASCVD event-risk reduction, and has been endorsed by multiple society recommendations or guidelines [13–16]. The objective of this analysis was to estimate the prevalence of TG levels ≥ 150 mg/

dl in statin-treated adults with diabetes or ASCVD in the US.

METHODS

This analysis included laboratory data, medical history, and prescription data from 40,617 subjects who participated in the US National Health and Nutrition Examination Survey (NHANES) spanning 8 years (four 2-year surveys; 2007–2014). The methodology for NHANES data collection has been described in detail [17]. Subjects who were ≥ 20 years old and had morning fasting (at least 8.5 h) TG values available were included in the analysis.

The prevalence of individuals with TG levels ≥ 150 mg/dl was calculated based on the actual number of participants in NHANES from 2007–2014, for the overall population, and according to statin use, as well as in key subgroups of statin-treated patients including those with LDL-C levels < 100 mg/dl, type 2 diabetes, ASCVD, and those with both type 2 diabetes and ASCVD. The weighted total number of patients in the US in millions was also estimated. Type 2 diabetes was defined as fasting glucose levels ≥ 126 mg/dl, non-fasting glucose levels ≥ 200 mg/dl, the use of insulin or other medications to lower blood sugar, or a diagnosis by a healthcare provider at age ≥ 30 years. LDL-C (mg/dl) was calculated using the Friedewald equation (total cholesterol − high-density lipoprotein cholesterol − [TG/5]).

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

RESULTS

The study sample included 40,617 individuals from the NHANES 2007–2014 survey. A total of 9593 subjects met the study entry criteria and were included in the analysis. This group was projected to represent 219.9 million Americans. A total of 2523 individuals from this group had TG levels ≥ 150 mg/dl. As shown in Table 1, this translates to a prevalence of 25.9%, representing 56.9 million Americans. Among statin-treated adults, the proportion with TG levels ≥ 150 mg/dl was 31.6% (12.3 million) and ranged from 27.6 to 39.5% for those who also had LDL-C controlled to < 100 mg/dl with statin therapy and type 2 diabetes or ASCVD (Table 1).

DISCUSSION

More than 25% of all US adults (56.9 million individuals) have TG levels ≥ 150 mg/dl, including 31.6% (12.3 million) of those already being treated with statins. In another recent analysis of this population, 70.5 million US adults were estimated to have TG levels ≥ 135 mg/dl [18]. This lower threshold of moderately elevated TG levels has also been associated with residual cardiovascular event risk, including patients with statin-controlled LDL-C [19]. Taken together, these results indicate a substantial healthcare burden in terms of both cost as well as morbidity and mortality associated with elevated TG levels.

Schwartz et al. [19] demonstrated a significant trend toward increased risk of both short- and long-term ASCVD events following acute coronary syndrome, according to progressively higher tertiles or quintiles of TG concentrations ($P = 0.03$ and $P < 0.001$, respectively). This study further reported that the adjusted risk of ASCVD events increased by 1.5 times between the highest (> 175 mg/dl) and lowest (≤ 80 mg/dl) quintiles of TG levels. The cardiovascular event risk associated with TG level, regardless of statin use, was investigated in Danish patients from the Copenhagen City Heart Study and the Copenhagen General Population Study. The results showed a significantly elevated risk of myocardial infarction in patients with TG levels between 89 and 176 mg/dl compared to those with TG levels < 89 mg/dl (HR 1.6; 95% CI 1.4–1.9), indicating substantial risk at lower TG levels [20].

In REDUCE-IT, the ASCVD event risk across strata of baseline TG levels (< 150 mg/dl, ≥ 150 mg/dl, < 200 mg/dl, and ≥ 200 mg/dl) in placebo-treated patients ranged from 21.0 to 22.6% [12]. In another analysis of this study

Table 1 Weighted prevalence of TG levels ≥ 150 mg/dl among adults ≥ 20 years of age in NHANES 2007–2014

	Prevalence, %	Patients with TG levels ≥ 150 mg/dl, millions[a]	Total number of patients, millions[a]
Overall	25.9	56.9	219.9
Statin treated	31.6	12.3	38.9
Statin treated and LDL-C < 100 mg/dl	27.6	6.0	21.7
Statin treated and diabetes	39.5	4.9	12.4
Statin treated and ASCVD	30.5	3.1	10.1
Statin treated and diabetes or ASCVD	34.4	6.4	18.6

ASCVD atherosclerotic cardiovascular disease, *LDL-C* low-density lipoprotein cholesterol, *NHANES* National Health and Nutrition Examination Survey, *TG* triglyceride

[a] Projected number of US adults

in which patients were stratified according to tertiles of baseline TG levels, ASCVD event risk ranged from 21.1% for those with TG ≤ 190 mg/dl to 23.7% for those with TG > 250 mg/dl [21]. The addition of icosapent ethyl consistently and significantly reduced ASCVD event risk in all TG strata [21]. After stratifying patients by tertiles of baseline TG levels, the associated HRs for the reduction of time to first ASCVD event risk or cardiovascular death with icosapent ethyl treatment were 0.79 (95% CI 0.66–0.94) for those with TG levels ≥ 81 to ≤ 190 mg/dl, 0.80 (95% CI 0.68–0.95) for TG levels > 190 to ≤ 250 mg/dl, and 0.68 (95% CI 0.57–0.80) for TG levels > 250 to ≤ 1401 mg/dl [21]. These results demonstrated that icosapent ethyl reduces ASCVD event risk irrespective of baseline or on-treatment TG levels. Researchers have suggested that anti-platelet and/or anti-inflammatory properties of EPA may help explain this event reduction, although further investigation is warranted [22]. Since the release of the results of REDUCE-IT, subsequent publications discussing health care guidelines have recognized the importance of adding icosapent ethyl therapy to patients with ASCVD or diabetes and multiple risk factors taking maximally tolerated statin therapy with LDL-C levels < 100 mg/dl and moderately elevated TG levels [23, 24].

Other large cardiovascular outcomes trials in patients with hypertriglyceridemia have failed to show ASCVD event-risk reduction with treatments given as adjuncts to statins. In the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) and the Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) studies, there was no difference between niacin and placebo in terms of endpoints related to cardiovascular events [25, 26]. Similarly, the Action to Control Cardiovascular Risk in Diabetes (ACCORD)–Lipid and the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) studies did not demonstrate any significant differences with fenofibrate treatment in their respective primary cardiovascular endpoints, despite improvements in lipid profiles [27, 28]. In the Vitamin D and Omega-3 Trial (VITAL), 1 g daily (460 mg of EPA and 380 mg of docosahexaenoic acid [DHA]) of concentrated fish oil capsules failed to reduce major adverse cardiovascular events among a primary prevention cohort with no previous history of cardiovascular disease despite a significant reduction in myocardial infarction [29]. Moreover, a meta-analysis of 18 randomized controlled trials indicated a non-significant reduction in coronary heart disease

risk with EPA + DHA overall (summary relative risk estimate [SRRE] 0.94; 95% CI 0.85–1.05), as well as nonsignificant relative risk reductions among patients with LDL-C levels ≥ 130 mg/dl (SRRE 0.86; 95% CI 0.76–0.98) and TG levels ≥ 150 mg/dl (SRRE 0.84; 95% CI 0.72–0.98) [30]. More recently, the Outcomes Study to Assess Statin Residual Risk Reduction With Epanova in High CV Risk Patients With Hypertriglyceridemia (STRENGTH, NCT02104817), which investigated the impact of adding 4 g/day EPA + DHA to statins, was recently stopped due to a low likelihood of demonstrating a benefit to the patients studied. Although the omega-3 fatty acids EPA and DHA are frequently conflated as having similar biological effects, the halting of the STRENGTH trial may be due to their differences in activity, doses utilized, and achieved blood levels [31]. In addition, given the fact that the majority of combination EPA + DHA trials have been negative to date [29, 32–36], it is possible that DHA exerts effects that may antagonize or even negate the benefit exerted by EPA. An ongoing clinical trial investigating a newer fibrate (pemafibrate) in patients with type 2 diabetes (Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes [PROMINENT]; NCT03071692) may be informative [37].

CONCLUSIONS

In summary, more than 12 million Americans are treated with a statin and have TG levels ≥ 150 mg/dl, a degree of hypertriglyceridemia associated with increased ASCVD event risk [8, 19, 20]. New approaches are needed to address residual ASCVD event risk in these patients, including lifestyle modification adherence measures and the use of evidence-based pharmacologic therapies shown to reduce ASCVD event risk. Icosapent ethyl is the first treatment to demonstrate a reduction in cardiovascular death and ischemic disease in statin-treated patients with elevated TG levels and established ASCVD or with type 2 diabetes plus additional risk factors, and should be considered when designing treatment plans for this population based on the expanded FDA indication for this agent.

ACKNOWLEDGEMENTS

Funding. The study, medical writing assistance, and the journals' rapid service fee were funded by Amarin Pharma Inc., Bridgewater, NJ, USA.

Medical Writing and Editorial Assistance. Medical writing assistance was provided by Peloton Advantage, LLC, an OPEN Health company, Parsippany, NJ, USA.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosures. Wenjun Fan has no relationships to disclose. Sephy Philip and Craig Granowitz are employees of Amarin Pharma, Inc. Peter P. Toth is a consultant and speaker for Amarin Pharma, Inc., Amgen, Kowa, and Novo Nordisk. Nathan D. Wong receives research support from Amarin Pharma, Inc., Amgen, Boehringer Ingelheim, Novo Nordisk, and Novartis, and has participated on advisory boards or speakers bureaus for Amarin Pharma, Inc., Sanofi, and Esperion.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Data Availability. The datasets generated during and/or analyzed during the current study are available in the National Health and Nutrition Examination Survey repository https://wwwn.cdc.gov/nchs/nhanes/Default.aspx.

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