

# A Real-World Study of the Risk of Cardiovascular Events and Atherosclerosis among Patients with Severe Hypertriglyceridemia

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## BACKGROUND

- Background:** Hypertriglyceridemia (HTG) is defined by elevated levels of circulating triglycerides (TG). Adults with HTG have an increased risk of cardiovascular (CV) events and atherosclerosis.<sup>1</sup> However, there is limited real-world evidence regarding the risk among patients at different levels of elevated TG.
- Objective:** To evaluate the risk of CV events and atherosclerosis among adults with mild-to-moderate HTG and severe HTG (sHTG), compared with normal TG levels.

## STUDY DESIGN

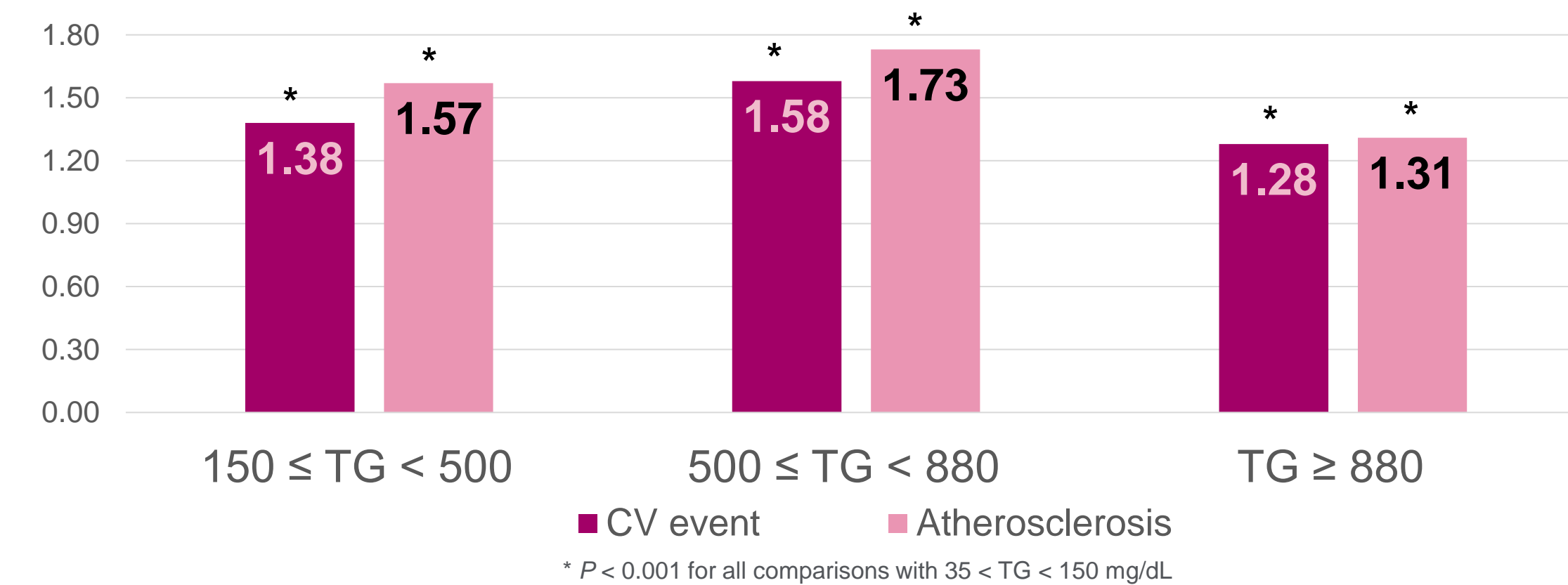
- Design:** Retrospective analysis of administrative claims and linked laboratory data from the Optum Research Database for the period between 01 January 2016 to 31 March 2022.
- Eligibility criteria:** Adults with ≥1 diagnostic test claim for serum/plasma TG. The index date was the date of earliest claim.
  - Continuous enrollment in commercial or Medicare Advantage plans with medical and pharmacy benefits for ≥ 12 months before and after the index date (baseline and follow-up).
- Patient stratification:** Patients were assigned to one of four cohorts based upon serum/plasma TG levels on the index date:
  - Normal TG (35 < TG < 150 mg/dL)
  - Mild-to-moderate HTG (150 ≤ TG < 500 mg/dL)
  - sHTG, divided into 500 ≤ TG < 880 mg/dL or TG ≥ 880 mg/dL sub-cohorts
  - Patients in the normal TG and mild-to-moderate HTG cohorts were randomly selected from their respective larger populations, and hence do not represent the epidemiological distributions of these populations.
- Outcomes:**
  - CV events (composite):** ≥ 1 claim with diagnoses of myocardial infarction not leading to death, unstable angina, acute coronary syndrome, stroke or transient ischemic attack, coronary or peripheral revascularization, or heart failure-specific hospitalization or emergency visit
  - Atherosclerosis:** ≥ 1 claim for atherosclerosis
- Statistical methods:**
  - Incidence rates were calculated per 100,000 person-years at risk. Kaplan-Meier analysis (for CV events and atherosclerosis) and adjusted Cox proportional hazards models (for CV events only) compared the risk of HTG or sHTG with normal TG.

**Table 1:** Baseline demographic and clinical data, by TG level\*

Characteristic	Normal (35 < TG < 150) n=46,676 (34.8%)	Mild-to-moderate HTG (150 ≤ TG < 500) n=54,090 (40.3%)	sHTG (500 ≤ TG < 880) n=28,556 (21.3%)	sHTG (≥ 880) n=4994 (3.7%)
Age (years), mean (SD)	54.7 (17.4%)	58.8 (15.3%)	55.2 (13.5%)	51.4 (11.9%)
Age ≥ 65 (%)	33.6%	41.0%	26.6%	14.3%
Female, n (%)	26,554 (56.9%)	26,013 (48.1%)	8399 (29.4%)	1126 (22.6%)
Baseline CV event, n (%)				
Stroke or transient ischemic attack	908 (2.0%)	1302 (2.4%)	615 (2.2%)	76 (1.5%)
Heart attack or unstable angina	372 (0.8%)	624 (1.2%)	418 (1.5%)	54 (1.1%)
Quan-Charlson comorbidity index (CCI) category <sup>2</sup> , n (%)				
CCI = 0	35,957 (77.0%)	36,659 (67.8%)	18,319 (64.2%)	3485 (69.8%)
CCI = 1-2	8816 (19.9%)	13,804 (25.5%)	7739 (27.1%)	1182 (23.7%)
CCI = 3-4	1459 (3.1%)	2805 (5.2%)	1860 (6.5%)	251 (5.0%)
CCI ≥ 5	444 (1.0%)	822 (1.5%)	638 (2.2%)	76 (1.5%)
Baseline comorbid conditions, n (%)				
Hypertension	16,109 (34.5%)	28,469 (52.6%)	16,671 (58.4%)	2692 (53.9%)
Other lipid metabolism disorders	14,253 (30.5%)	28,212 (52.2%)	18,066 (63.3%)	2888 (57.8%)
Diabetes (all types)	4488 (9.6%)	11,830 (21.9%)	10,427 (36.5%)	1874 (37.5%)
Hyperglyceridemia	238 (0.5%)	1086 (2.0%)	2304 (8.1%)	523 (10.5%)
Hypothyroidism	5438 (11.7%)	8215 (15.2%)	3984 (14.0%)	527 (10.6%)
Liver disease	1776 (3.8%)	3517 (6.5%)	2822 (9.9%)	509 (10.2%)
Chronic kidney disease	2502 (5.4%)	5134 (9.5%)	3270 (11.5%)	423 (8.5%)
TG-lowering medications, n (%)				
Statins	10,353 (22.2%)	20,278 (37.5%)	11,765 (41.2%)	1820 (36.4%)
Fibrates	394 (0.8%)	1827 (3.4%)	3642 (12.8%)	833 (16.7%)
Omega-3 fatty acids	95 (0.2%)	365 (0.7%)	1091 (3.8%)	231 (4.6%)
Total cholesterol ≥ 240 mg/dL	3345 (7.3%)	8419 (15.8%)	10,210 (36.1%)	1959 (56.4%)

\* TG levels are in mg/dL; TG, serum/plasma triglycerides; HTG, hypertriglyceridemia; sHTG, severe hypertriglyceridemia; CV, cardiovascular

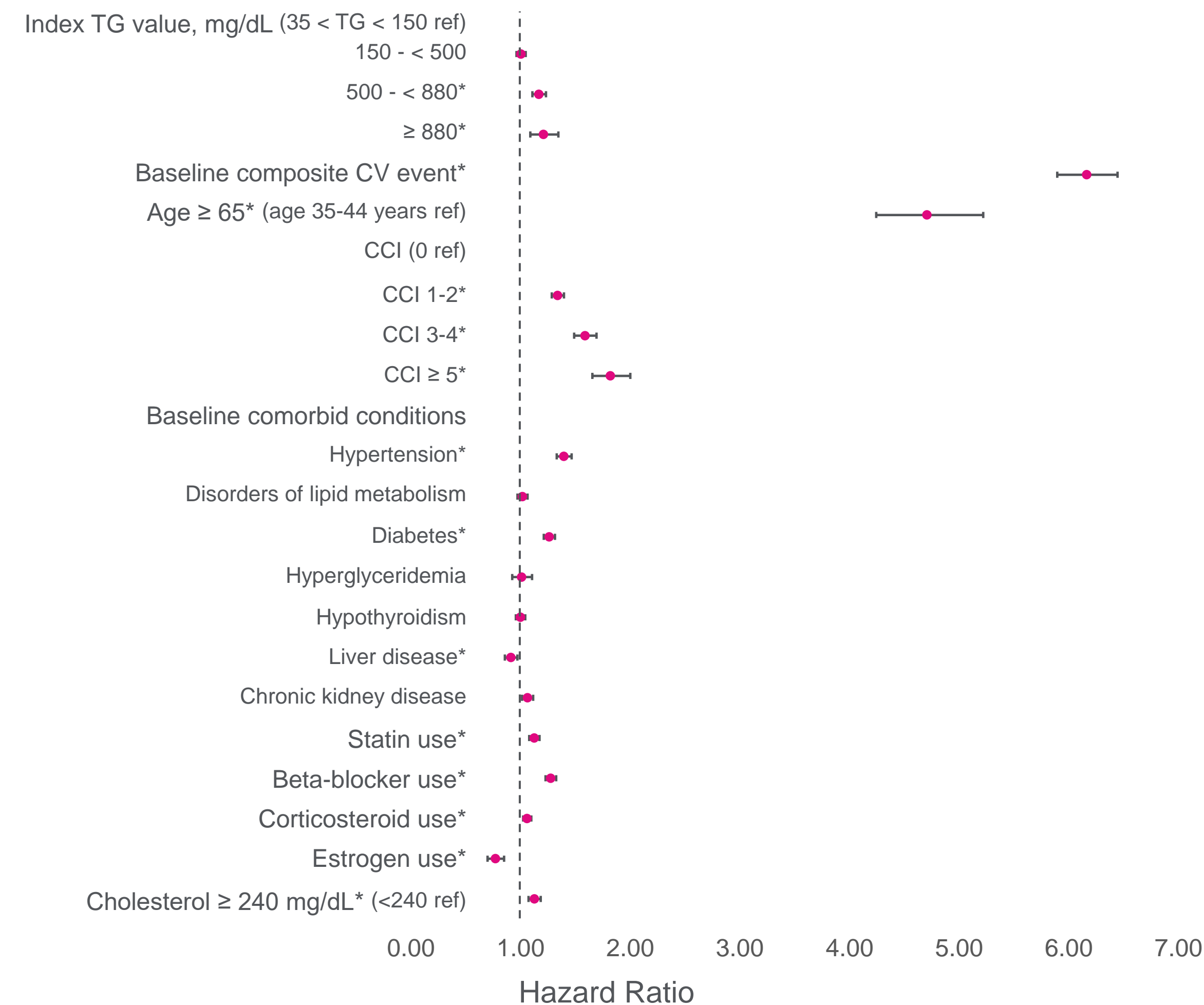
**Figure 1:** Incidence rate ratios for CV events and atherosclerosis during follow-up, by TG level



## RESULTS

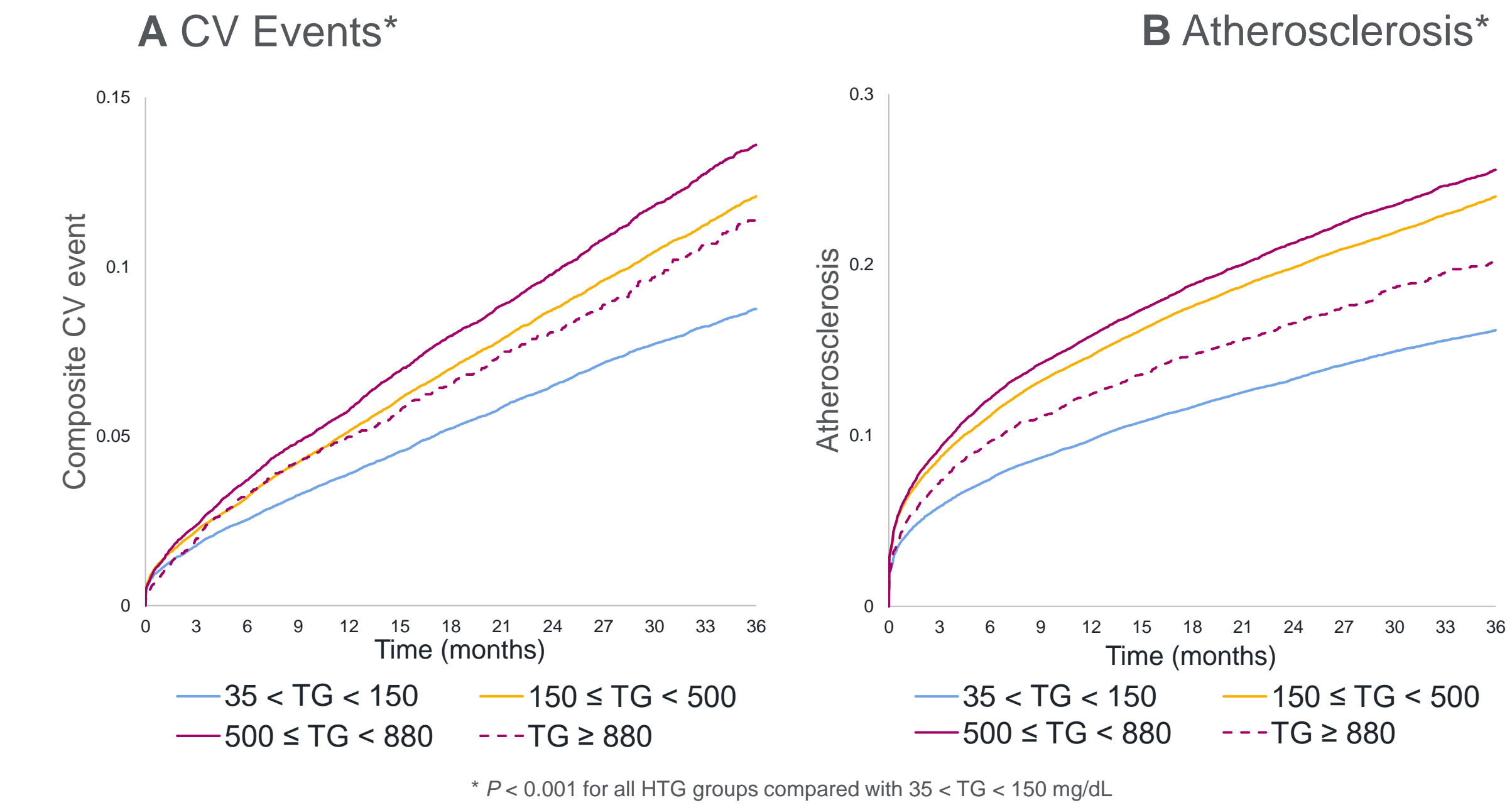
- Study sample:** A total of 134,316 patients were included; the mean (SD) follow-up time was 987 (446) days.
- 3-Year cumulative incidences (Fig. 3):**
  - CV events:** The 3-year cumulative incidences were 8.8%, 12.1%, 13.6%, and 11.4% for the normal, mild-to-moderate HTG, 500 ≤ TG < 880 sHTG, and sHTG ≥ 880 groups, respectively (*P* < 0.001 for all HTG groups compared with 35 < TG < 150 mg/dL).
  - Atherosclerosis:** The 3-year cumulative incidences were 16.2%, 24.0%, 25.6%, and 20.1% for the normal, mild-to-moderate HTG, 500 ≤ TG < 880 sHTG, and sHTG ≥ 880 groups, respectively (*P* < 0.001 for all HTG groups compared with 35 < TG < 150 mg/dL).

**Figure 2:** Adjusted<sup>^</sup> Cox proportional hazards ratios (95% CI) for CV events throughout variable follow-up



\* P < 0.01, compared with reference group, no history (for baseline comorbidities), or no use (for medications); <sup>^</sup>In addition to the variables listed above, other covariates in the regression model included baseline acute pancreatitis (AP); geographic region; and baseline use of fibrates, omega-3 fatty acids, niacin, protein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists, thiazide diuretics, immunosuppressants, bile acid sequestrants, retinoids, and class 1a and 1b AP-inducing medications; CCI, Quan-Charlson comorbidity index

**Figure 3:** Cumulative incidence of CV events and atherosclerosis during follow-up, by TG level



\* P < 0.001 for all HTG groups compared with 35 < TG < 150 mg/dL

## CONCLUSIONS

- sHTG was associated with significantly increased risk of CV events and atherosclerosis, compared with patients at normal TG levels.
- 3-year cumulative incidence of CV events and atherosclerosis was significantly higher in the mild-to-moderate HTG and sHTG cohorts, compared with normal TG.
- The 500 ≤ TG < 880 and TG ≥ 880 sHTG sub-cohorts had a 16.8% and 21.0% higher risk of CV events, respectively, when compared with normal TG and adjusted for baseline covariates.
- Baseline CV events and age ≥ 65 were the largest predictors of CV events.
- Other significant predictors of CV events included CCI > 0, hypertension, diabetes (all types), total cholesterol ≥ 240 mg/dL, and the use of statins and beta-blockers.

## DISCLOSURES

ASK and MVL are employees of Ionis Pharmaceuticals and own company stock; KB and QA are employees of Optum/United Health Group (UHG), which was contracted to conduct this research; QA owns UHG Stock; SB is an investigator and consultant for Ionis Pharmaceuticals; DS is a consultant for Ionis Pharmaceuticals.

## REFERENCES

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