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FASTTRACK CLINICAL RESEARCH
Lipids

Real-world risk of cardiovascular outcomes associated with hypertriglyceridaemia among individuals with atherosclerotic cardiovascular disease and potential eligibility for emerging therapies

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Aims Hypertriglyceridaemia in patients with atherosclerotic cardiovascular disease (ASCVD) has been in focus following the REDUCE-IT trial showing benefit with icosapent ethyl. Among individuals with prevalent ASCVD, we sought to quantify the contemporary, real-world risk of ASCVD events associated with hypertriglyceridaemia, as well as estimate icosapent ethyl eligibility and compare trial participants with REDUCE-IT-like individuals in the population.

Methods and results We examined data from 2 424 865 adults with lipid panels in the Ontario population. Among those with prevalent ASCVD, we examined adjusted associations between triglyceride (TG) and ASCVD events (first occurrence of myocardial infarction, unstable angina, stroke or transient ischaemic attack, coronary revascularization, or cardiovascular death). The proportion of patients with ASCVD potentially eligible for icosapent ethyl was estimated as those with TG 135–499 mg/dL (1.52–5.63 mmol/L) and low-density lipoprotein cholesterol (LDLc) 41–100 mg/dL (1.06–2.59 mmol/L), similar to the lipid cut-offs in REDUCE-IT, and their demographics and event rates examined. Among 196 717 individuals with ASCVD, median age was 69 years and 30% were female. A total of 24 097 composite ASCVD events occurred over a mean (standard deviation) 2.9 (0.5) years of follow-up. Increasing TG was associated with a graded, progressively higher hazard of ASCVD events. Twenty-five percent (49 886) of individuals with ASCVD had hypertriglyceridaemia and controlled LDLc; these patients were demographically similar to those in REDUCE-IT with comparable event rates.

Conclusions Among patients with ASCVD, hypertriglyceridaemia is common, and is associated with higher ASCVD risk across a range of TG. It is possible that as many as one in four patients with ASCVD may be candidates for emerging therapies.

Keywords Atherosclerosis • Cardiovascular disease • Hypertriglyceridaemia • Icosapent ethyl • Secondary prevention • Remnant cholesterol • Triglyceride

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Introduction

Levels of low-density lipoprotein cholesterol (LDLc) have been in steady decline in many resource-rich settings in response to lifestyle and pharmacologic interventions.[1,2] Despite this progress, atherosclerotic cardiovascular disease (ASCVD) events continue to occur frequently.[3] This has compelled an interest in treating individuals with residually elevated triglyceride (TG), who have higher concentrations of atherogenic cholesterol carried by circulating triglyceride-rich lipoproteins (TRLs),[4–6] also referred to as remnant cholesterol.[4,7]

Although elevated TG has been associated with cardiovascular outcomes, most studies were conducted in patients without established ASCVD, prior to the contemporary era. The role of reducing residual risk by targeting TG reductions has been reignited following the results of a recent Phase III randomized clinical trial of icosapent ethyl [ethyl eicosapentaenoic acid (EPA), a derivative of the omega-3 fatty acid EPA], among patients with or at high risk for ASCVD—the Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT) trial.[8] Additionally, two large, Phase 3 trials of other compounds in patients with elevated cardiovascular risk and hypertriglyceridaemia are ongoing.[9,10] Given that clinical trials frequently enrol a highly selected population of patients, placing such trials in the context of real-world observations can help to inform assessment of clinical need, external generalizability of trial results, and eventually inform healthcare practice and policy decisions. Hence, to provide population-based context for emerging strategies to reduce TG among individuals with established ASCVD, we aimed to (i) assess the prevalence of hypertriglyceridaemia in a contemporary, real-world population of individuals with prevalent ASCVD and examine relationships with events; (ii) estimate the proportion of patients with high TG and controlled LDLc who may be candidates for emerging therapies in contemporary clinical practice; and (iii) compare REDUCE-IT trial participants to 'real-world' patients to inform external generalizability of the REDUCE-IT findings.

Methods

Data sources

The analyses were conducted in the CANHEART cohort, representing a linkage of 17 individual-level electronic databases, were linked together using unique encoded personal identifiers and analysed at ICES, as has been described previously.[11,12] Key data (and their sources) were: (i) patient identifiers (the Ontario Registered Persons Database); (ii) cardiac risk factors and comorbidities [the Canadian Institute for Health Information (CIHI) Discharge Abstract Database, the Ontario Diabetes Database, the Ontario Hypertension Database, and the Ontario Cancer Registry]; (iii) pharmacotherapy (Ontario Drug Benefit prescription database covering individuals ≥65 years of age); (iv) lipid and other laboratory results [the Ontario Laboratory Information System (which captures >90% of outpatient labs in Ontario)]; (v) vital status (the Registrar General of Ontario Vital Statistics Database); and (vi) other health status, health determinants, and health care utilization information [Canadian Community Health Survey (CCHS)].

Study sample

Ontario residents alive as of 1 January 2011, who were ≥40 years of age at the time, and had a valid Ontario Health Insurance Plan number were eligible for inclusion. We identified individuals with full lipid panels (including TG, LDLc, HDLc, and total cholesterol) in the year prior cohort inception. We then identified patients who had prior ASCVD by identifying individuals with a history of myocardial infarction (MI), unstable angina, non-haemorrhagic stroke, peripheral arterial disease, or prior coronary revascularization through percutaneous coronary intervention or coronary artery bypass surgery. Individuals with major life expectancy-limiting conditions (long-term haemodialysis, dementia, or metastatic cancer within the past 5 years) as well as those residing in a nursing home were excluded. Identification of prevalent conditions was based on International Classification of Diseases 10th revision in the CIHI-DAD.[11,12]

Exposures and outcomes

Triglyceride concentrations measured 1 year prior to the inception date (from 1 January 2010 to 31 December 2010) were used as the primary exposure. For patients who had more than one measurement, the value closest to 1 January 2011 was used.

The primary outcome was the first occurrence of MI, unstable angina, stroke or transient ischaemic attack (TIA), coronary revascularization, or cardiovascular death. The components of the primary outcome were also examined individually.

Prevalence of hypertriglyceridaemia and potential eligibility for icosapent ethyl

We examined the proportion of patients in our cohort who had TG 135–499 mg/dL (1.52–5.63 mmol/L) and LDLc 41–100 mg/dL (1.06–2.59 mmol/L), reflective of a pragmatic approximation of the lipid-defined REDUCE-IT inclusion criteria. REDUCE-IT enrolled patients with (70.7%) or at high risk for (29.3%) ASCVD. During REDUCE-IT trial enrolment, the inclusion criteria of the trial were modified to increase the minimum TG for entry from 150 (±10% variation, i.e., 135 mg/dL) to 200 mg/dL (1.52–2.26 mmol/L), to enrol a higher-risk population. However, given that the potential benefit of icosapent ethyl was similar among those with TG above and below 200 mg/dL in a *post hoc* analysis,[8] we used 135 mg/dL (1.52 mmol/L) as the minimum TG to define potential eligibility in our cohort. We also sought to examine to what extent individuals with TG 135–499 mg/dL (1.52–5.63 mmol/L) and LDLc 41–100 mg/dL (1.06–2.59 mmol/L) in our cohort were reflective of REDUCE-IT trial participants by comparing demographic variables and event rates.

Statistical analysis

Triglyceride was non-normally distributed (Supplementary material online, *Figure S1*) and therefore the study cohort was stratified based on index TG categories: <1, 1.0–1.5, 1.5–2.0, 2.0–2.5, 2.5–3.0, 3.0–3.5, 3.5–4.0, and >4.0 mmol/L. Demographic variables were examined across exposure categories and compared using one-way analysis of variance for continuous variables and χ^2 test for categorical variables. Event rates were standardized by age and sex, calculated by direct standardization using the 2006 Canadian population as the reference population. We also examined adjusted Cox proportional hazards models for ASCVD outcomes in relation to TG categories. Models were adjusted for age, sex, income, LDLc, baseline diabetes, and baseline hypertension. We examined risks in the overall cohort, as well as stratified by sex, diabetes status, and LDLc categories [≥ or < median LDLc, 74 mg/dL (1.9 mmol/L)]. A two-sided *P*-value <0.05 was considered significant. Analyses were performed using SAS (version 9.3, SAS Institute Inc., Cary, NC, USA). The use of data in this project was authorized under section 45 of Ontario's Personal Health Information

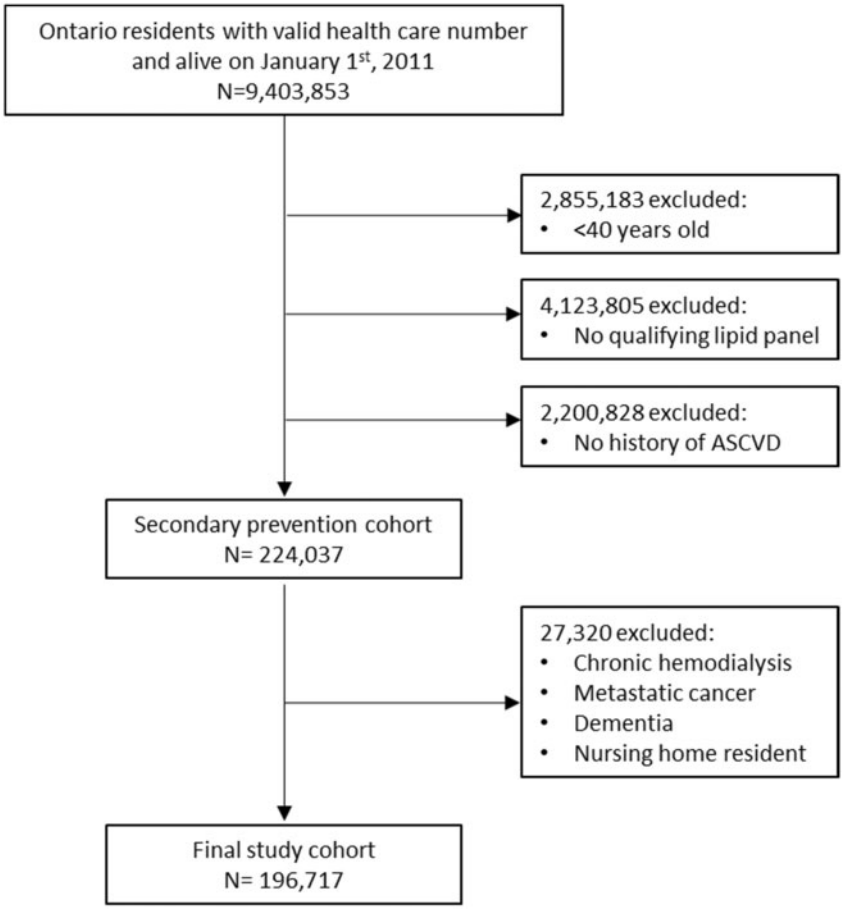


Figure 1 Flow diagram of cohort construction.

Protection Act, which does not require review by a Research Ethics Board.

Results

The study cohort was derived from 9 403 853 individuals in the CANHEART cohort[11] as of 1 January 2011 (*Figure 1*). Among these individuals, 2 424 865 were ≥ 40 years of age as of the inception data and had an eligible lipid panel. Among these, 196 717 had established ASCVD (*Table 1*) after application of the exclusion criteria, and comprised the study cohort.

Cohort demographics

The median [interquartile range (IQR)] age of the study cohort was 66 (58–73) years and 30.1% were female (*Table 1*). The median (IQR) TG and LDLc concentrations were 1.3 (0.9–1.8) mmol/L [115 (80–159) mg/dL] and 1.9 (1.6–2.4) mmol/L [168 (142–212) mg/dL], respectively; 23.9% of participants had a TG ≥ 2.0 mmol/L [177 mg/dL]. The prevalence of diabetes was progressively higher among individuals with higher TG levels, increasing steadily from 36.4% in the lowest to 61.8% in the highest stratum (*Table 1*). Levels of HDLc were progressively lower among individuals with higher TG. Among 2708 individuals with CCHS data, the proportions with ideal body mass index and ideal physical activity levels were progressively lower among those with increasing levels of TG. Among those older than 66 years with available prescription drug information, rates of non-statin lipid-lowering therapies were: ezetimibe (11.7%), fenofibrate (2.4%), gemfibrozil (0.1%), bezafibrate (0.1%), and niacin (0.6%).

Relationship between triglyceride and atherosclerotic cardiovascular disease

Over a median 3.0 years, representing 563 307 patient-years of follow-up, a total of 24 097 composite ASCVD events occurred. The age- and sex-standardized primary outcome (first occurrence of MI, unstable angina, stroke or TIA, coronary revascularization, or cardiovascular death) rate was 38.6 per 1000 person-years and ranged from 32.2 to 57.6 per 1000 person-years for those in the lowest to highest TG category, respectively (*Table 2*).

In comparison to individuals with TG < 1.0 mmol/L (the reference group), increasing TG concentration was associated with increasing graded rate of the primary composite outcome (*Figure 2*), such that rate among individuals with TG > 4.0 mmol/L was 52% higher [adjusted hazard ratio (HR) 1.52, 95% confidence interval 1.36–1.71; $P < 0.0001$] than those in this lowest TG category. Increased rates of

Table 1 **Baseline demographic characteristics**

	Triglyceride (mmol/L) category								
	<1	1–1.5	1.5–2	2–2.5	2.5–3	3–3.5	3.5–4	≥4	Total
	N = 57 287	*N* = 63 773	*N* = 37 732	*N* = 18 890	*N* = 9452	*N* = 4875	*N* = 2764	*N* = 1944	*N* = 196 717
Clinical variables									
Age	67.0 (59.0–75.0)	66.0 (59.0–74.0)	65.0 (58.0–73.0)	64.0 (57.0–72.0)	63.0 (56.0–71.0)	63.0 (55.0–70.0)	61.0 (54.0–69.0)	61.0 (53.0–68.0)	66.0 (58.0–73.0)
Female	25.7%	30.5%	33.2%	33.8%	32.8%	32.8%	30.8%	30.8%	30.1%
Diabetes mellitus	20 881 (36.4%)	27 477 (43.1%)	18 333 (48.6%)	9946 (52.7%)	5245 (55.5%)	2790 (57.2%)	1666 (60.3%)	1202 (61.8%)	87 540 (44.5%)
Hypertension	45 723 (79.8%)	52 814 (82.8%)	31 767 (84.2%)	16 060 (85.0%)	8019 (84.8%)	4169 (85.5%)	2343 (84.8%)	1637 (84.2%)	162 532 (82.6%)
MI	28 363 (49.5%)	31 883 (50.0%)	18 834 (49.9%)	9484 (50.2%)	4683 (49.5%)	2486 (51.0%)	1481 (53.6%)	983 (50.6%)	98 197 (49.9%)
Revascularization	24 638 (64.2%)	26 503 (63.0%)	14 784 (62.4%)	6832 (61.1%)	6832 (61.1%)	1607 (61.7%)	831 (60.8%)	527 (58.7%)	527 (58.7%)
Unstable angina	19 955 (34.8%)	23 696 (37.2%)	14 541 (38.5%)	7463 (39.5%)	3771 (39.9%)	2001 (41.0%)	1110 (40.2%)	732 (37.7%)	73 269 (37.2%)
Non-haemorrhagic stroke	6177 (10.8%)	6388 (10.0%)	3592 (9.5%)	1773 (9.4%)	862 (9.1%)	443 (9.1%)	220 (8.0%)	183 (9.4%)	19 638 (10.0%)
PAD	2639 (6.9%)	3273 (7.8%)	2029 (8.6%)	1080 (9.7%)	517 (9.8%)	266 (10.2%)	169 (12.4%)	109 (12.1%)	10 082 (8.0%)
CHF	6506 (11.4%)	7765 (12.2%)	4605 (12.2%)	2369 (12.5%)	1188 (12.6%)	673 (13.8%)	401 (14.5%)	263 (13.5%)	23 770 (12.1%)
Income quintile									
Lowest	17.1%	19.0%	19.6%	20.3%	22.4%	21.9%	24.4%	24.2%	–
Highest	22.0%	19.6%	18.3%	17.4%	16.3%	16.7%	14.8%	14.7%	–
Laboratory variables									
Total cholesterol	3.5 (3.0–4.0)	3.7 (3.2–4.3)	3.9 (3.4–4.5)	4.1 (3.6–4.8)	4.3 (3.7–5.1)	4.4 (3.8–5.3)	4.6 (4.0–5.4)	4.7 (4.1–5.7)	3.8 (3.3–4.4)
Triglyceride	0.8 (0.7–0.9)	1.2 (1.1–1.4)	1.7 (1.6–1.8)	2.2 (2.1–2.3)	2.7 (2.6–2.8)	3.2 (3.1–3.3)	3.7 (3.6–3.8)	4.3 (4.1–4.4)	1.3 (0.9–1.8)
LDLc	1.8 (1.5–2.2)	1.9 (1.6–2.4)	2.0 (1.6–2.6)	2.0 (1.6–2.6)	2.0 (1.5–2.7)	1.9 (1.4–2.7)	1.9 (1.4–2.7)	1.8 (1.2–2.7)	1.9 (1.6–2.4)
Non-HDLc	2.2 (1.8–2.6)	2.5 (2.1–3.0)	2.8 (2.4–3.3)	3.0 (2.6–3.6)	3.2 (2.8–3.9)	3.4 (2.9–4.2)	3.6 (3.1–4.4)	3.8 (3.2–4.6)	2.6 (2.1–3.2)
Calculated RC	0.4 (0.3–0.4)	0.6 (0.5–0.6)	0.8 (0.7–0.8)	1.0 (1.0–1.1)	1.2 (1.2–1.3)	1.5 (1.4–1.5)	1.7 (1.6–1.8)	1.9 (1.9–2.0)	0.6 (0.4–0.8)
HDLc	1.3 (1.0–1.5)	1.1 (1.0–1.4)	1.1 (0.9–1.3)	1.0 (0.9–1.2)	1.0 (0.9–1.2)	1.0 (0.8–1.1)	0.9 (0.8–1.1)	0.9 (0.8–1.1)	1.1 (0.9–1.4)
CCHS lifestyle variables	*N* = 767	*N* = 878	*N* = 559	*N* = 267	*N* = 113	*N* = 66	*N* = 33	*N* = 25	*N* = 2708
Ideal alcohol consumption	92.6%	92.7%	89.2%	88.8%	90.1%	83.3%	87.9%	88.0%	91.1%
Ideal BMI	42.4%	28.7%	20.0%	18.3%	18.0%	14.1%	*	*	28.4%
Ideal diet	39.3%	31.4%	28.8%	35.0%	39.6%	27.4%	*	*	33.4%
Ideal physical activity	55.1%	43.0%	45.2%	42.3%	38.9%	45.3%	25.0%	32.0%	46.4%
Ideal smoking history	83.5%	80.4%	79.8%	76.8%	78.8%	80.3%	69.7%	88.0%	80.7%

Data are presented as median (IQR) or proportions.
BMI, body mass index; CCHS, Canadian Community Health Survey; CHF, congestive heart failure; MI, myocardial infarction; PAD, peripheral arterial disease.
*Due to privacy legislation of Ontario, Canada, these data have been masked because of the small number of subjects to prevent re-identification of subjects.

Table 2 Age and sex-standardized (to the 2006 Ontario census population) incidence rates (per 1000) for the primary composite outcome (first occurrence of cardiovascular death, myocardial infarction, unstable angina, arterial revascularization, or ischaemic stroke) and its components

	Triglyceride (mmol/L) category								
	<1	1–1.5	1.5–2	2–2.5	2.5–3	3–3.5	3.5–4	≥4	Total
Outcome	N = 57 287	N = 63 773	N = 37 732	N = 18 890	N = 9452	N = 4875	N = 2764	N = 1944	N = 196 717
Primary outcome									
Composite	32.16	36.81	42.19	42.12	45.67	52.22	54.03	57.56	38.62
Secondary outcomes									
Cardiovascular death	7.11	7.12	7.59	7.73	7.71	9.38	10.87	11.29	7.52
MI/unstable angina	13.65	16.12	19.1	20.13	20.51	25.61	26.01	24.64	17.18
Revascularization	16.68	20.8	25.15	24.7	25.92	30.32	30.8	34.51	21.82
Non-haemorrhagic stroke	3.69	3.82	4.12	3.02	4.98	4.3	5.8	3.96	3.89
Additional outcomes									
All-cause death	18.12	18.33	18.59	18.69	20.5	21.34	23.23	23.22	18.75
CHF	7.07	6.87	8.19	8.78	8.97	9.36	10.42	12.63	7.67

Data are presented as median (IQR) or proportions.
CHF, congestive heart failure; MI, myocardial infarction.

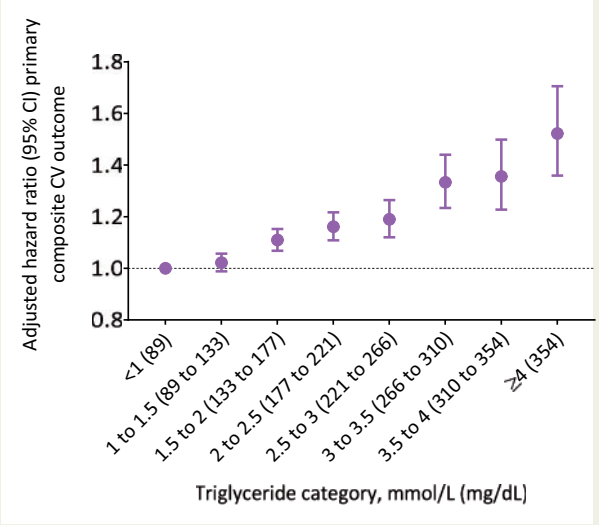


Figure 2 Adjusted hazard ratios (95% confidence intervals) for the composite outcome (cardiovascular death, myocardial infarction, unstable angina, arterial revascularization, or ischaemic stroke) by varying levels of triglyceride among 196 717 individuals with atherosclerotic cardiovascular disease. Models were adjusted for age, sex, income, low-density lipoprotein cholesterol, baseline diabetes, and baseline hypertension. CI, confidence interval; HR, hazard ratio.

MI/unstable angina as well as of revascularization primarily contributed to this composite risk. The increased adjusted HRs associated with TG were similar among those with and without diabetes mellitus (*Table 3*). The magnitude of risk appeared similar among women compared with men and among those with LDLc ≥1.9 mmol/L compared with those <1.9 mmol/L, although statistical evidence of effect modification was observed in this large sample ($P = 0.03$ and $P = 0.001$, respectively).

Hypertriglyceridaemia and controlled low-density lipoprotein cholesterol in the population

Among individuals in Ontario with prevalent ASCVD ($N = 196\,717$), 49 886 (25.4%) had TG of 135–499 mg/dL (1.52–5.63 mmol/L) and LDLc of 41–100 mg/dL (1.06–2.59 mmol/L). These individuals were similar to REDUCE-IT trial participants, in terms of age, sex, and history of prevalent diabetes (*Table 4*). Overall, 6327 (12.7%) of these individuals experienced the primary composite ASCVD outcome during a mean 2.9 years of follow-up.

Discussion

Our study was designed to provide population-level context for emerging strategies to reduce TG among individuals with prevalent ASCVD. As in other cohorts,[13] the distribution of TG in almost 200 000 patients with ASCVD was right skewed. We observed that the risk of major adverse cardiovascular events was associated with increasing levels of TG across a broad range of TG concentrations. These risks were qualitatively similar among men and women, diabetics and non-diabetics, and among those with controlled vs. elevated LDLc. Approximately 25% of patients in this secondary prevention cohort had hypertriglyceridaemia and controlled LDLc, and might qualify for icosapent ethyl. REDUCE-IT trial participants generally resembled those in the population with hypertriglyceridaemia and controlled LDLc, with generally similar event rates over follow-up.

To our knowledge, this is the largest, contemporary, population-based cohort study to focus on risk associated with elevated TG specifically among those with established ASCVD. Several retrospective analyses of completed randomized clinical trials have demonstrated associations between TG and outcomes in selected trial-based populations, including TNT,[14] PROVE-IT,[15] IDEAL,[14] dal-OUTCOMES,[16]

Table 3 Adjusted hazard ratios (95% confidence intervals) for the composite major adverse cardiovascular event outcome (cardiovascular death, myocardial infarction, unstable angina, arterial revascularization, or ischaemic stroke) by varying levels of triglyceride among stratified by subgroups of interest

	Adjusted HR (95% CI) 5-component MACE[a]							
	Triglyceride (mmol/L) category							
	<1	1–1.5	1.5–2	2–2.5	2.5–3	3–3.5	3.5–4	≥4
Overall								
	1.0	1.02 (0.99–1.06)	1.11 (1.07–1.15)	1.16 (1.11–1.22)	1.19 (1.12–1.26)	1.33 (1.23–1.50)	1.36 (1.23–1.50)	1.52 (1.36–1.71)
Sex								
Male	1.0	1.01 (0.97–1.05)	1.09 (1.05–1.14)	1.15 (1.09–1.22)	1.14 (1.06–1.23)	1.32 (1.20–1.45)	1.32 (1.17–1.49)	1.46 (1.27–1.68)
Female	1.0	1.04 (0.97–1.11)	1.13 (1.06–1.22)	1.18 (1.08–1.29)	1.28 (1.15–1.43)	1.35 (1.18–1.59)	1.44 (1.20–1.72)	1.64 (1.35–2.00)
Diabetes mellitus								
Yes	1.0	1.01 (0.96–1.06)	1.08 (1.02–1.14)	1.18 (1.11–1.26)	1.20 (1.11–1.30)	1.29 (1.17–1.43)	1.33 (1.17–1.50)	1.51 (1.31–1.73)
No	1.0	1.03 (0.99–1.08)	1.14 (1.08–1.21)	1.12 (1.04–1.21)	1.15 (1.05–1.27)	1.39 (1.22–1.58)	1.40 (1.17–1.66)	1.51 (1.23–1.85)
LDLc (mmol/L)								
<1.9	1.0	1.00 (0.96–1.05)	1.07 (1.01–1.13)	1.11 (1.04–1.19)	1.13 (1.03–1.24)	1.26 (1.12–1.41)	1.31 (1.14–1.51)	1.50 (1.28–1.75)
≥1.9	1.0	1.07 (1.02–1.13)	1.20 (1.14–1.27)	1.27 (1.19–1.36)	1.33 (1.22–1.44)	1.50 (1.35–1.67)	1.49 (1.30–1.71)	1.65 (1.40–1.94)

CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular event.
[a]Five-component MACE includes first occurrence of cardiovascular death, myocardial infarction, unstable angina, arterial revascularization, or ischaemic stroke. Models were adjusted for age, sex, income, LDLc (except LDLc subgroup analysis), baseline diabetes (except baseline diabetes subgroup analysis), and baseline hypertension. Results of testing for the interaction between TG category and strata were: sex ($P = 0.03$); diabetes mellitus ($P = 0.42$); LDLc ($P = 0.001$).

and MIRACL.[16] Additionally, two recent observational studies restricted to individuals reflective of REDUCE-IT inclusion criteria—in mixed primary and secondary prevention settings—have also observed associations between elevated TG and ASCVD.[17,18] A recent study in the CLARITY registry also supported the external generalizability of the REDUCE-IT trial, suggesting that 15% of patients with established coronary artery disease may be eligible for therapy.[19] Our study importantly extends this previous work, first by virtue of its large, contemporary, population-based setting, and by examining potential population-level eligibility for emerging therapies and comparing 'real-world' patients with those in the recent trial. Our results support an important role for TG-related risk in the contemporary population, and highlight the potential scope for intervention. Overall, a sizable proportion (1 in 4) of individuals with ASCVD may be candidates for such emerging therapies.

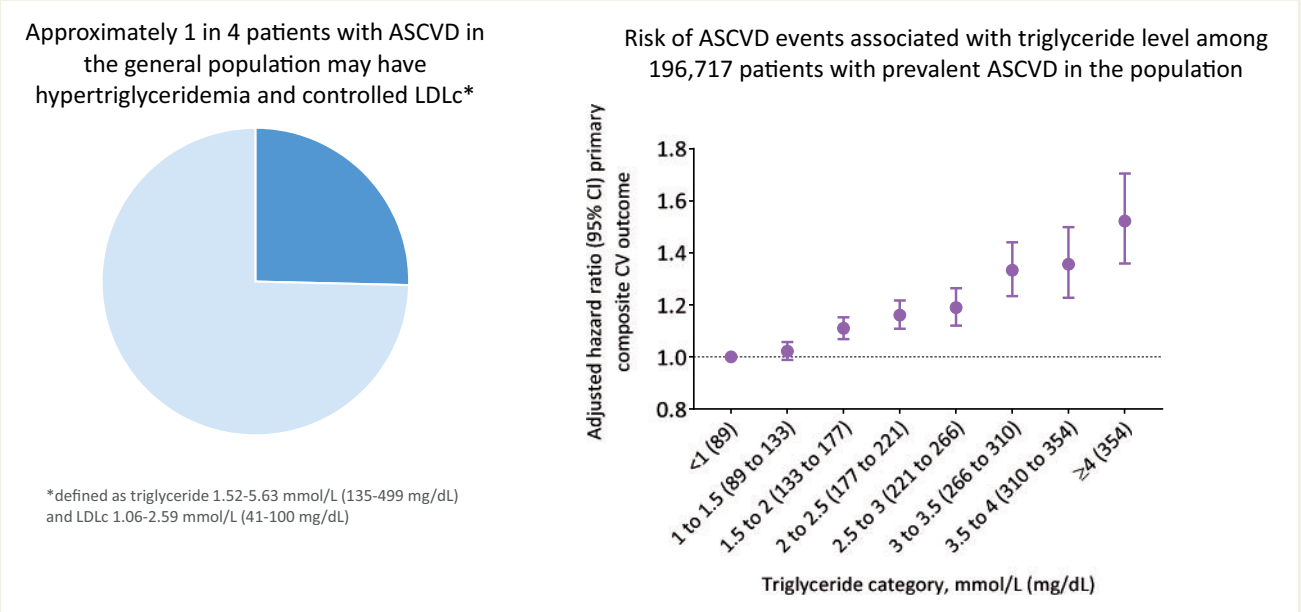
Our findings support the assertion that the risk of ASCVD events among patients with established ASCVD and LDLc at goal remains unacceptably high. This residual risk may reflect alternative pathways of atherogenesis not captured by LDLc, including those related to TRLs and related remnant cholesterol. Such unmet clinical need has prompted several recent trials targeting individuals with or at high risk for ASCVD who have controlled LDLc and hypertriglyceridaemia.[8–10] In the recently completed REDUCE-IT trial, a 25% relative risk reduction in composite ASCVD events was observed with icosapent ethyl (ethyl EPA), a derivative of the omega-3 fatty acid EPA.[8] A secondary analysis further highlighted the potential cumulative benefit of icosapent ethyl in reducing the cumulative burden of ASCVD events.[20] Given that clinical trials often enrol a highly selected population of patients, our study sought to investigate the trial's potential external generalizability. Participants in the REDUCE-IT trial demographically resembled those with hypertriglyceridaemia and controlled LDLc in the population. While follow-up differed between REDUCE-IT and our CANHEART population, and REDUCE-IT enrolled patients both with and at high risk for ASCVD, event rates were generally similar in both populations. In CANHEART, TG-associated risk was evident among men and women, diabetics and non-diabetics, and among those with controlled vs. elevated LDLc. Similarly, in REDUCE-IT, efficacy of icosapent ethyl was similar in these subgroups.

Serum TG level identifies the presence of potentially atherogenic TRLs, which are not reflected by LDLc concentration but contain (remnant) cholesterol which evidence suggests is atherogenic. Genetic epidemiologic studies have supported a causal role of TG-related mediators in ASCVD[5]—observations now borne out in REDUCE-IT. Triglyceride was cited a likely ASCVD risk factor by the 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias,[21] although recommendations for treatment were not strong, at the time deriving primarily from subgroup or *post hoc* analyses. Similar conclusions were reached by the 2016 European Guidelines on Cardiovascular Disease Prevention in Clinical Practice.[22] Our findings and those from REDUCE-IT support, and may extend, such guidance. However, important questions remain regarding to what extent the benefit observed in REDUCE-IT was mediated by TG vs. a combination with other potentially favourable effects of icosapent ethyl. Additionally, the increase in high sensitivity C-reactive protein and LDLc in the placebo (mineral oil) group raised questions as to whether risk may have been inflated among those in the placebo group. Interestingly, the benefit of icosapent ethyl was independent of achieved TG level. Further analyses, including mediation analyses, in REDUCE-IT will support efforts to better understand the potential mechanisms of benefit. Prior studies have suggested that the atherogenicity of TRLs may vary based on size-defined TRL subclass distributions,[23,24] and hence examining the

Table 4 Demographic and outcomes among patients with hypertriglyceridaemia (135–499 mg/dL) and controlled low-density lipoprotein cholesterol (41–100 mg/dL) in the CANHEART prevalent cardiovascular disease cohort and among participants in the REDUCE-IT trial of icosapent ethyl

	CANHEART ASCVD cohort with TG 135–499 mg/dL and LDLc 41–100 mg/dL	REDUCE-IT participants[a]	
		Icosapent ethyl	Placebo
N	49 886	4089	4090
Demographics			
Age	68.0 (61.0–75.0)	64.0 (57.0–69.0)	64.0 (57.0–69.0)
Male	68.8	71.6	70.8
Diabetes mellitus	54.1	58.6	58.5
Statin use[b]	95.5	100%[c]	
TG	177 (151–221)	217 (177–272)	216 (176–274)
LDLc	70 (58–81)	74 (35–46)	76 (63–89)
HDLc	39 (35–46)	40 (35–46)	40 (35–46)
Follow-up			
Follow-up (years)	2.9	4.9	
Primary composite event rate[d]	6327/49886 (12.7)	559/2892 (19.3)[d]	738/2893 (25.5)

Data are proportions (%) or median (IQR).
[a]Demographic data are for all REDUCE-IT participants, who included 29.3% of patients without but at high risk for ASCVD; event rates reflect only those with prevalent ASCVD (secondary prevention stratum).
[b]Ascertainable only among those ≥66 years old (*N* = 28 863).
[c]Statin use was required for entry into REDUCE-IT, but data on statin use were missing in 0.4% of participants in the overall trial.
[d]Composite of first myocardial infarction, cardiovascular death, hospitalization for unstable angina, coronary revascularization, or ischaemic stroke; in REDUCE-IT event rate is for the secondary prevention stratum.



Take home figure Proportion of patients with atherosclerotic cardiovascular disease in the Ontario, Canada, population with hypertriglyceridaemia and controlled LDLc (left panel). The adjusted association between triglyceride level and cardiovascular events among individuals with atherosclerotic cardiovascular disease in the Ontario, Canada, population (right panel).

effects of icosapent ethyl on the circulating TRL milieu may shed light on potential mechanism of benefit.

Our study has several potential limitations. First, we were unable to ascertain data on lipid-lowering therapy usage among individuals under 66 years old. However, the majority in the secondary prevention cohort would be expected to be prescribed lipid-lowering therapy per clinical practice guidelines. Indeed, among older patients in whom we could ascertain statin prescription, the proportion of

individuals prescribed statins was 80% in the overall cohort and 95% among REDUCE-IT-like patients. All multivariable models were adjusted for each patients' LDLc. Furthermore, stratifying the overall cohort by LDLc level revealed significant, graded increases in ASCVD risk as TG increased in those with both high and low levels of LDLc (although there was statistical evidence of effect modification). These findings suggest that TG-related risk may be present in both those with and without controlled LDLc. Similarly, in REDUCE-IT, there was no evidence of heterogeneity in treatment effect by LDLc ($P = 0.62$) or statin use ($P = 0.12$), suggesting that TG-related risk and the potential beneficial effects of therapy may not be appreciably affected by concomitant statin prescription. However, despite adjustment for LDLc, without complete ascertainment of statin use we cannot exclude the potential influence of possibly variable statin use on these results. Additionally, our study was not designed to examine risk associated with TG, nor to estimate potential eligibility for icosapent ethyl, among individuals who had no ASCVD owing to the fact that we had insufficient information to recreate the REDUCE-IT entry criteria. Further studies of potential eligibility for emerging therapies targeting TG reduction in primary prevention are warranted. Additionally, inadequate information was available to apply the exclusion criteria in REDUCE-IT, and as such some individuals in the secondary prevention cohort in CANHEART may not have qualified for the REDUCE-IT trial, although it bears noting that trial exclusion may not one day imply non-candidacy for therapy. Furthermore, given the biologic variability in TG, the REDUCE-IT trial used an arithmetic mean of TG levels obtained on two sequential visits; our population-based cohort was not amenable to reproducing such an approach using data from 'real-world' clinical practice. Finally, it was not known if samples were collected during fasting or non-fasting states, although national guidelines recommendations at the time were for fasting,[25] and therefore it is presumed that levels generally reflect fasting state. Non-fasting patients may possibly be over-represented among those with higher TG levels. We could not explore potential non-compliance with the—at the time—national recommendations for fasting lipid sampling, although non-compliance with this recommendation could theoretically reflect patients more likely to be non-compliant with other medical care and therefore at higher risk. It is anticipated that such potential individuals, with adequate fasting, would have lower TG levels.

Conclusion

In this large, contemporary, population-based cohort, we observed that among individuals with established ASCVD, hypertriglyceridaemia is associated with ASCVD events across a spectrum of TG levels. We determined that a sizable proportion of patients with ASCVD in 'real-world' clinical settings have hypertriglyceridaemia and controlled LDLc, and may potentially be candidates for interventions to further reduce residual cardiovascular risk.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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