European Journal of Internal Medicine 111 (2023) 90–96

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original article

Hypertriglyceridemia is associated with decline of estimated glomerular filtration rate and risk of end-stage kidney disease in a real-word Italian cohort: Evidence from the TG-RENAL Study

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ARTICLE INFO

Keywords:
eGFR reduction
End-stage kidney disease
Hypertriglyceridemia
Real-world evidence
Triglycerides

ABSTRACT

Background: This analysis investigated the role of hypertriglyceridemia on renal function decline and development of end-stage kidney disease (ESKD) in a real-world clinical setting.
Methods: A retrospective analysis using administrative databases of 3 Italian Local Health Units was performed searching patients with at least one plasma triglyceride (TG) measurement between 2013 and June 2020, followed-up until June 2021. Outcome measures included reduction in estimated glomerular filtration rate (eGFR) ≥30% from baseline and ESKD onset. Subjects with normal (normal-TG), high (HTG) and very high TG levels (vHTG) (respectively <150 mg/dL, 150–500 mg/dL and >500 mg/dL) were comparatively evaluated.
Results: Overall 45,000 subjects (39,935 normal-TGs, 5,029 HTG and 36 vHTG) with baseline eGFR of 96.0 ± 66.4 mL/min were considered. The incidence of eGFR reduction was 27.1 and 31.1 and 35.1 per 1000 person-years, in normal-TG, HTG and vHTG subjects, respectively ($P<0.01$). The incidence of ESKD was 0.7 and 0.9 per 1000 person-years, in normal-TG and HTG/vHTG subjects, respectively ($P<0.01$). Univariate and multivariate analyses revealed that HTG subjects had a risk of eGFR reduction or ESKD occurrence (composite endpoint) increased by 48% compared to normal-TG subjects (adjusted OR:1.485, 95%CI 1.300–1.696; $P<0.001$). Moreover, each 50 mg/dL increase in TG levels resulted in significantly greater risk of eGFR reduction (OR:1.062, 95% CI 1.039–1.086 $P<0.001$) and ESKD (OR:1.174, 95%CI 1.070–1.289, $P = 0.001$).
Conclusions: This real-word analysis in a large cohort of individuals with low-to-moderate cardiovascular risk suggests that moderate-to-severe elevation of plasma TG levels is associated with a significantly increased risk of long-term kidney function deterioration.

1. Introduction

In addition to the role in promoting the atherogenic process, hypertriglyceridemia (HTG), has been implicated in the development and progression of renal damage [1–4]. Indeed, the abnormal deposition of lipids within the intrarenal vascular bed has been shown to contribute to glomerular injury by mechanism involving the increased oxidative stress and the production of proinflammatory cytokines as well as the hyperactivity of growth factors [5,6]. Furthermore, data from intervention studies suggested that pharmacologic reduction of plasma triglycerides (TGs) may provide some degree of renal protection. For example, in the FIELD study conducted in diabetic patients treated with

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[1] The members of the Local Health Units Group are listed in the Acknowledgement section of the manuscript.

https://doi.org/10.1016/j.ejim.2023.02.019
Received 6 December 2022; Received in revised form 17 February 2023; Accepted 20 February 2023
Available online 10 March 2023

the TG-lowering medication fenofibrate, it was observed that the reduction of TGs was accompanied by the reduction of albuminuria and the attenuation of estimated glomerular filtration rate (eGFR) loss overtime [7]. More recently, in the REDUCE-IT trial, the cardiovascular protection determined by the TG-lowering drug icosapent ethyl fatty acid was maintained in the subgroup of subjects with chronic kidney disease (CKD) [8].

Different cutoff values have been suggested by taskforces and national societies to define HTG. However, there is a consensus on using a value of TG>150 mg/dL (>1.7 mmol/L) as a meaningful clinical threshold for HTG [9]. This condition, which represents a relatively common finding in clinical practice, could be used to identify individuals at increased cardiovascular and renal risk especially among those not requiring statin therapy.

Real-world evidence of the relationship between HTG and renal outcomes are limited. However, further studies on renal outcomes associated with HTG are of importance, in the light of the increasing prevalence of conditions which are known to be related to both CKD and HTG dyslipidemia, such as obesity, hypertension and metabolic syndrome [10]. Moreover, addressing this issue may further raise awareness among general practitioners and other clinicians about the importance of evaluating TGs in each individual as well as of therapeutic targeting HTG.

In the present study, by using electronic health records contained in integrated administrative databases, we looked at the relationship between TG levels and renal outcomes in a retrospective, observational, longitudinal cohort study including subjects at relatively low cardiovascular risk.

2. Materials and methods

2.1. Data sources

A retrospective cohort analysis using administrative and laboratory databases of 3 Italian Local Health Units (LHU) was performed, including about 700,000 health-assisted subjects. The following database were assessed for the present study: (i) beneficiaries database, which includes data on subjects' characteristics; (ii) pharmaceuticals database, which includes the Anatomical-Therapeutic-Chemical (ATC) code of the drug dispensed, the number of packs dispensed, the number of units per pack, the dose, the unit cost per pack, and the prescription date; (iii) hospitalization database, which includes all hospitalization data with the primary and secondary discharge diagnosis codes classified according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM); (iv) laboratory tests and specialist visits database; (v) laboratory test value database.

In full compliance with the Italian Code of Protection of personal data, databases were anonymized, and each patient was identified by an anonymous code, which permitted the electronic linkage between these databases. Data were extracted by administrative staff and no identifiers related to subjects were provided to researchers. Results of analyses were produced as aggregated summaries to prevent, either directly or indirectly, any link to individual subjects. Informed consent was not required for using encrypted retrospective information. According to the Italian law [11], this analysis has been notified to the local Ethical Committee of the LHU involved in the study.

2.2. Cohort definition and data collection

All individuals with at least one TG measurement between January 1, 2013 and June 30, 2020 (inclusion period) were considered. Subjects were excluded if they had: (i) substantial variation in TG measurements during follow-up period, i.e. TG measurements not included in the categorization criteria defined for this study (see details on group categorization in the following paragraphs); (ii) at least one prescription of omega 3 fatty acids or fibrates during both the characterization and the follow-up period; (iii) at least one prescription of antiplatelet drugs during the characterization period because it may be considered as a proxy of vascular disease; (iv) before inclusion at least one hospitalization for myocardial infarction or any other of the following: angina pectoris, chronic cardiac ischemia, occlusion and stenosis of carotid arteries and transient cerebral ischemia; (v) previous hospitalization for chronic kidney disease (CKD), end-stage renal disease (ESKD), of dialysis. Moreover, patients without at least one eGFR detection during the characterization period (the last available, i.e. baseline value) and one eGFR detection during the observation period, the last available, were excluded.

Out of 700,000 health-assisted population included in the study, 45,000 subjects were included in the present analysis. The flowchart of the study population selection is presented in Fig. 1.

The index-date was defined for all included subjects as the data of the first TGs measurement during the inclusion period; starting from this date, individuals were retrospectively characterized up to 12 months, and events occurring until June 30, 2021 were considered (characterization and follow-up periods, respectively).

Results of fasting lipid profiles measured in each district laboratories following standard procedures were extracted from laboratory databases [12]. Individuals were categorized into 3 groups based on TG measurements available in the follow-up period: (i) "normal TG" group, those with all TGs measurements <150 mg/dL), (ii) "high TG" group, those with all TGs measurements between 150 and 500 mg/dL (HTG) and (iii) "very high TG" group, those with all measurements >500 mg/dL) (vHTG).

During the characterization period, data on baseline individuals' characteristics, including demographics (age and gender) and medical history (hospital admission, procedures, prescribed drugs, and comorbidities) were collected. Comorbidities were identified based upon the diagnoses at hospital discharge (both primary and secondary diagnosis according to the ICD-9-CM codes) derived from hospitalization database. Also drug prescriptions (ATC codes) derived from pharmaceutical databases, were used to identify comorbidities considering the use of specific medications as a proxy of diseases. No data on obesity or alcohol use were available. The following diagnoses during the characterization period were considered: (i) acute pancreatitis (ICD-9-CM code: 577), (ii) CKD (ICD-9-CM codes: 585.3, 585.4, 585.5, 585.6), (iii) chronic obstructive pulmonary disease (COPD) (ATC code: R03), (iv) previous atherosclerotic cardiovascular disease (ASCVD) defined as admissions for myocardial infarction (ICD-9-CM code: 410), angina pectoris (ICD-9-CM code: 413), chronic cardiac ischemia (ICD-9-CM code: 414), occlusion and stenosis of the pre-cerebral arteries (ICD-9-CM code: 433), occlusion and significant stenosis of cerebral arteries (ICD-9-CM code: 434), transient cerebral ischemia (435), cerebral circulatory disorders (ICD-9-CM code: 436), other and poorly defined cerebral vasculopathies (ICD-9-CM code: 437), atherosclerosis (ICD-9-CM code: 440), aneurysm of the aorta (ICD-9-CM code: 441), other aneurysms (ICD-9-CM code: 442), and vascular diseases (ICD-9-CM code: 443).

The prescription of the following drugs was analysed during the 12-month characterization period (at least one prescription): antidiabetic medications (ATC code A10), statins (ATC codes C10AA, C10BA02), anti-hypertensive medications (ATC codes C03, C07, C08, C09), and anticoagulant medications (ATC codes B10AA, B10AB). Moreover, the last available measurements of total cholesterol (mg/dL) and high-density lipoprotein cholesterol (HDL-C) (mg/dL) before index date were retrieved.

Renal outcomes were defined as a 30% eGFR reduction as compared with baseline, reaching ESKD or a composite of both previous endpoints. ESKD (including dialysis) was defined by hospitalization discharge diagnosis [ICD-9-CM codes 585.6, V560 (primary or secondary diagnosis)], by procedures (39.95, 54.98, primary or secondary procedures), or specialistic codes (39.95, 54.98).

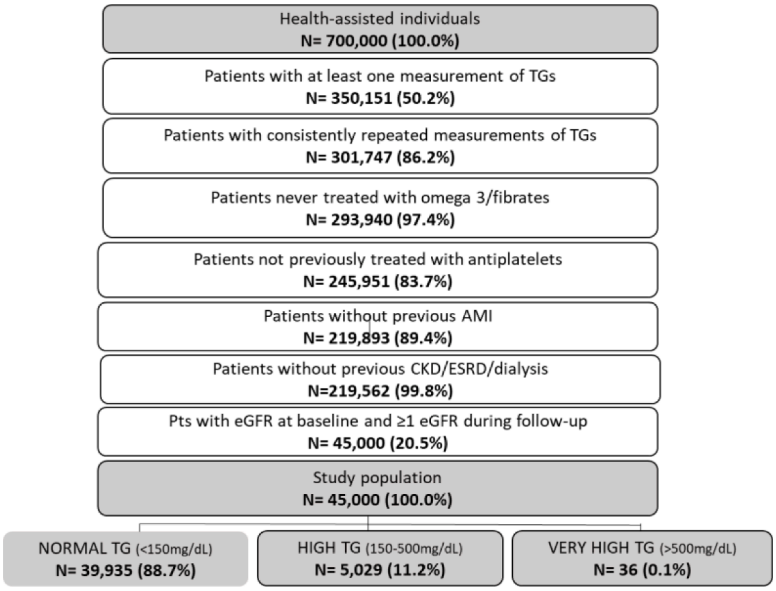

Fig. 1. Study population flowchart.
Abbreviations: AMI, acute myocardial infarction; CKD, Chronic Kidney Disease; ESKD, End-stage Kidney Disease; TG, total plasma triglycerides.

2.3. Statistical analysis

Continuous data are presented as means with standard deviation or median and interquartile range and categorical variables as numbers and percentages. The independent samples *t*-test and analysis of variance test were used to compare continuous variables and the chi-square test was used to compare categorical variables. Non-parametric Mann-Whitney U test was used for not normally distributed variables. Multivariate analysis of the association of severity grade of HTG with long-term adverse outcomes was performed using the Cox proportional hazards model, giving hazard ratios and 95% confidence intervals (95% CI). Covariates for hazard ratios adjustment were identified after a forward stepwise selection as follows: age, gender, hypertension, diabetes, renal function, antidiabetic medications, statin use, anti-hypertensive medications, anticoagulant medications, baseline total cholesterol, baseline HDL cholesterol, baseline eGFR.

The results were considered statistically significant when the P-value was <0.05. STATA SE software version 17.1 was used for statistical analyses

3. Results

Among the enrolled subjects, 88.7% (39,935) were categorized in the normal TG group, 11.2% (5029) in the HTG group and 0.1% (36) in the vHTG group. All subjects had on average at least two TGs measurements recorded during follow-up.

The baseline characteristics of the whole study population as well as according to TGs categories are reported in Table 1.

Overall, the included subjects had a mean age of 59.0 ± 21.1 years and 44% were males. Renal function was normal (eGFR 96.0 ± 66.4 mL/min) and the prevalence of ASCVD, as expected by selection criteria, was very low. In comparison with the other groups, vHTG subjects were significantly younger and showed higher prevalence of male gender. Individuals with normal TGs had TG levels of 85.6 ± 23.7 mg/dL, while those with HTG and vHTG had TG levels of 216.2 ± 54.3 mg/dL and 691.8 ± 191.2 mg/dL, respectively, a difference that was highly statistically significant ($P<0.001$). Concordantly, mean levels of non-HDL-C, which reflects the concentration of all TG-rich lipoprotein particles in the blood, were significantly higher in both groups of hypertriglyceridemic in comparison with normal TG individuals. Similarly, plasma levels of total cholesterol (TC) were significantly raised in HTG and vHTG individuals in comparison with normal TG subjects. Given the inverse correlation between TGs and HDL-C levels, the latter showed a clear progressive reduction from individuals with normal toward those with very high TGs. As low-density lipoprotein cholesterol (LDL-C) concentrations were calculated by Friedwald's formula, they could not be reliably estimated among individuals with very high TG levels. However, LDL-C levels were significantly elevated in high versus normal TG individuals.

Interestingly, individuals with vHTG showed a significantly reduced prevalence of history of COPD in comparison with the other groups. Overall, the prevalence of history of acute pancreatitis was very small and did not differ between groups. In the whole study group, only a small percentage of individuals (<10%) were prescribed with statins and antidiabetic treatments and slightly more than one third were using anti-hypertensive medications. When the different therapies were examined according to the TG categories, individuals with HTG but not those with vHTG tended to show higher use of statins and hypertensive medications in comparison with normal TG individuals. On the contrary, both individuals in the HTG and vHTG categories showed a significantly higher use of antidiabetic medications in comparison with those in the normal TG group, thus suggesting an increased prevalence of diabetes among the high TG group. Anticoagulant medications also showed a limited use in the whole study cohort, and it did not display differences between groups.

Table 2 reports the incidence of renal outcomes according to TG categories. During a follow-up period of 4.2 ± 2.2 years, 4632, 594 and 4 subjects were reported to show a greater than 30% loss of eGFR in the normal, HTG and vHTG subgroups, respectively. This determined an incidence rate/1000-person years of 27.1, 31.1 and 35.1 in the three groups, respectively ($P<0.01$ for trend). Moreover, a significantly higher incidence rate/1000-person years of ESKD in the high TG group as compared to the normal TG group was also recorded (0.9 vs 0.7; $P<0.01$). When both renal outcomes (i.e. >30% GFR loss and ESKD) were combined (composite renal outcome) there was a linear trend toward greater incidence of worse outcome in the subgroups of subjects with progressively higher TG levels (27.4, 31.5 and 35.1 events per 1000 person-years in the group with normal, high and very high TG, respectively) (Table 2).

On the average, subjects who developed worse renal outcomes were older at baseline and showed slightly higher TG levels and lower total as well as LDL and HDL cholesterol (Table 3).

Table 1
Baseline clinical characteristics of study cohort according to triglycerides categories. Continuous variables are presented as means with standard deviation and categorical variables as numbers and percentages.

	Overall population	Normal TG	HTG	vHTG	P value
Population, n (%)	45,000	39,935 (88.7)	5029 (11.2)	36 (0.08)	
No. of TG measurements, mean (SD)	3.4 (2.8)	3.5 (2.9)	2.5 (2.2)	1.3 (0.6)	<0.001
Demographic characteristics					
Age, years, mean (SD)	59.0 (21.1)	58.9 (21.3)	60.0 (18.8)	54.4 (14.9)	<0.001
Male gender, n (%)	19,681 (43.7)	17,141 (42.9)	2512 (50.0)	28 (77.8)	<0.001
Plasma lipids, mg/dL, mean (SD)					
TG, average during the observational period	100.7 (53.2)	85.6 (23.7)	216.2 (54.3)	691.8 (191.2)	<0.001
TG, last measurement prior to index-date	102.5 (64.3)	91.1 (36.4)	211.6 (89.7)	1110.8 (1446.5)	<0.001
Total cholesterol, last measurement prior to index-date	196.4 (40.0)	195.0 (39.0)	209.2 (45.3)	278.6 (123.1)	<0.001
Non-HDL cholesterol, last measurement prior to index-date	136.4 (37.4)	133.4 (35.4)	165.6 (42.6)	242.8 (119.8)	0.152
HDL cholesterol, last measurement prior to index-date	60.8 (17.4)	62.5 (16.9)	44.0 (13.0)	35.8 (7.2)	<0.001
LDL cholesterol, last measurement prior to index-date	116.3 (34.4)	115.5 (33.4)	124.5 (41.0)	59.1 (148.9)	<0.001
Other biomarkers mean (SD)					
HbA1c, last measurement prior index-date, mmol/mol	48.9 (16.0)	48.4 (15.7)	51.4 (17.3)	65.2 (22.6)	<0.001
Plasma creatinine, last measurement prior index-date, mg/dL	0.9 (0.5)	0.9 (0.4)	1.0 (0.7)	1.0 (0.4)	<0.001
eGFR, last measurement prior index-date, mL/min/1.73 m^2	96.0 (66.4)	96.6 (66.2)	91.0 (67.9)	90.7 (29.8)	<0.001
Medications, n (%)					
Statins	4176 (9.3)	3553 (8.9)	620 (12.3)	NI	<0.001
Anticoagulants	5913 (13.1)	5183 (13.0)	727 (14.5)	NI	<0.010
Antihypertensives	17,640 (39.2)	15,256 (38.2)	2371 (47.1)	13 (36.1)	<0.001
Antidiabetics	4129 (9.2)	3427 (8.6)	694 (13.8)	8 (22.2)	<0.001
Comorbidities, n (%)					
Acute pancreatitis	175 (0.4)	153 (0.4)	21 (0.4)	NI	0.066
COPD	7027 (15.6)	6289 (15.7)	731 (14.5)	7 (19.4)	0.068
ASCVD	2264 (5.0)	1968 (4.9)	293 (5.8)	NI	<0.050
Follow up, years, mean (SD)	4.2 (2.2)	4.3 (2.2)	3.8 (2.1)	3.2 (2.6)	<0.001

Abbreviations: GFR, glomerular filtration rate; ESKD, end-stage renal disease; COPD, chronic obstructive pulmonary disease; ASCVD, atherosclerotic cardiovascular disease.

Furthermore, those who went on to lose a greater amount of eGFR overtime had slightly higher HbA1c levels and comparable serum creatinine (but higher eGFR values) at baseline and were receiving a greater amount of cardiovascular therapeutic agents, namely statins, anticoagulants, antihypertensives and glucose lowering drugs. Finally, they were more likely to have had a greater burden of comorbidities, such as COPD and ASCVD in the past.

Table 2
Renal outcome: incidence of eGFR reduction ≥30%, ESKD and either one of the previous (composite endpoint).

	Normal TG N = 39,935	High TG N = 5029	Very high TG N = 36	P value
eGFR reduction ≥30%				
Patients with events (n)	4632	594	4	
Person years of follow up	171,082	19,116	114	
Incidence rate/1000-person years	27.1	31.1	35.1	<0.01
Follow-up, years, mean (SD)	4.2 (2.2)	3.7 (2.2)	3.2 (2.6)	
ESKD				
Patients with events (n)	121	18	NI	
Person years of follow up	171,082	19,116		
Incidence rate/1000-person years	0.7	0.9		<0.01
Follow-up, years, mean (SD)	4.3 (2.2)	3.8 (2.1)		
Composite outcomes				
Patients with events (n)	4681	602	4	
Person years of follow up	171,082	19,116	114	
Incidence rate/1000-person years	27.4	31.5	35.1	<0.01
Follow-up, years, mean (SD)	4.2 (2.2)	3.7 (2.2)	3.2 (2.6)	

After adjustment for multiple variables, the estimates of association between high TGs and renal outcomes remained highly statistically significant (Table 4). Indeed, in univariate and multivariate analysis, respectively, individuals with HTG had a 18% (OR: 1.181, 95%CI 1.084 - 1.287, $P<0.001$) and 49.8% (OR: 1.498, 95%CI 1.309 – 1.714, $P<0.001$) increased risk of eGFR reduction.

Furthermore, in univariate and multivariate analysis, respectively, subjects with HTG had 18% (OR: 1.182, 95%CI 1.085 – 1.286, $P<0.001$) and 48.5% (OR:1.485; 95%CI 1.300 – 1.696, $P<0.001$) increased risk to develop the composite renal endpoint. Also the risk of ESKD increased along with higher levels of TGs, even though the risk estimates reached the statistical significance only in the vHTG group. Finally, the risk of developing the composite renal outcome during follow-up in subjects with HTG was increased by 18% (OR: 1.182, 95% CI 1.085 – 1.286, $P<0.001$) in univariate and by 48.5% (OR:1.485; 95% CI 1.300 – 1.696, $P<0.001$) in multivariate analysis.

Moreover, among conventional risk factors estimated by using as proxy the reported, use of disease-specific medications, diabetes was significantly associated with a 28% (OR:1.281, 95%CI 1.184 - 1.386, $P<0.001$) increased risk to develop eGFR reduction while hypertension did not significantly predict the risk of developing eGFR reduction (OR: 1.061, 95%CI 0.958–1.175, $P = 0.258$) (data not shown).

4. Discussion

In this retrospective, observational longitudinal cohort study involving 45,000 individuals in the setting of local health services in Italy, we found that HTG was associated with a significant long-time risk of deterioration of renal function. Subjects with progressively higher TG values (normal to high and very high) showed an increasing incidence of a 30% eGFR loss (from 27 to 31 and up to 35 events for 1000-person years, $P<0.01$). These findings persisted even after controlling for several demographic and clinical confounders. The risk of adverse renal outcome associated with HTG was further supported by looking at a much solid renal endpoint such as ESKD as well as a composite of eGFR loss and/or ESKD. It is noteworthy that these figures were obtained in a cohort at relatively low cardiovascular risk as shown by the projected 10-year incidence of ASCVD events of 7%.

CKD is an insidious, largely underestimated long term complication in subjects with atherogenic profile and other cardiovascular risk conditions such as diabetes, hypertension and dyslipidemia, including HTG

Table 3
Baseline clinical characteristics of study cohort on the basis of renal outcome. Abbreviations: GFR, glomerular filtration rate; ESKD, end-stage renal disease; COPD, chronic obstructive pulmonary disease; ASCVD, atherosclerotic cardiovascular disease. * eGFR reduction [identified the comparison of eGFR value at baseline (last value before the index-date) with the last available value assessed during the follow-up)].

	eGFR reduction <30%*	eGFR reduction ≥30%*	P value	ESKD_NO	ESKD_YES	P value
Population, n (%)	39,770	5230		44,860	140	
Demographic characteristics						
Age, years, mean (SD)	58.0 (20.5)	66.5 (23.5)	<0.001	59.0 (21.1)	68.8 (14.5)	<0.001
Male gender, n (%)	17,367 (43.7)	2314 (44.2)	0.430	19,593 (43.7)	88 (62.9)	<0.001
Plasma lipids and other markers						
TG, mg/dL, average during the observational period, mean (SD)	100.5 (53.3)	102.3 (52.1)	<0.050	100.7 (53.0)	113.9 (92.0)	<0.010
TG, mg/dL, last measurement prior to index-dare, mean (SD)	101.4 (63.9)	112.4 (67.3)	<0.001	102.4 (64.3)	121.2 (73.1)	0.094
Total cholesterol, mg/dL, last measurement prior to index-date, mean (SD)	197.4 (39.7)	186.7 (41.5)	<0.001	196.4 (39.9)	182.6 (41.4)	<0.050
Non-HDL cholesterol, mg/dL, last measurement prior to index-date, mean (SD)	137.1 (37.4)	129.7 (37.2)	0.967	136.4 (37.4)	124.7 (37.1)	<0.050
HDL cholesterol, mg/dL, last measurement prior to index-date, mean (SD)	61.2 (17.3)	57.3 (18.6)	<0.001	60.8 (17.4)	56.5 (21.2)	0.135
LDL cholesterol, mg/dL, last measurement prior to index-date, mean (SD)	117.2 (34.3)	107.7 (34.2)	<0.001	116.3 (34.4)	102.3 (35.5)	<0.050
HbA1c, mmol/mol, last measurement prior index-date, mean (SD)	48.6 (16.0)	50.1 (15.9)	<0.050	48.8 (15.9)	56.0 (21.3)	<0.050
Creatinine, mg/dL, last measurement prior index-date, mean (SD)	0.9 (0.5)	0.9 (0.5)	0.792	0.9 (0.4)	3.0 (2.9)	<0.001
eGFR, mL/min/1.73m^2, last measurement prior index-date, mean (SD)	93.6 (51.4)	114.3 (132.0)	<0.001	96.1 (66.4)	44.5 (36.0)	<0.001
Medications						
Statins, n (%)	3608 (9.1)	568 (10.9)	<0.001	4151 (9.3)	25 (17.9)	<0.001
Anticoagulants, n (%)	4723 (11.9)	1190 (22.8)	<0.001	5885 (13.1)	28 (20.0)	<0.050
Antihypertensives, n (%)	14,776 (37.2)	2864 (54.8)	<0.001	17,541 (39.1)	99 (70.7)	<0.001
Antidiabetics, n (%)	3338 (8.4)	791 (15.1)	<0.001	4101 (9.1)	28 (20.0)	<0.001
Comorbidities						
Acute pancreatitis, n (%)	150 (0.4)	25 (0.5)	0.271	174 (0.4)	NI	0.536
COPD, n (%)	5959 (15.0)	1068 (20.4)	<0.001	7004 (15.6)	23 (16.4)	0.791
ASCVD, n (%)	1717 (4.3)	547 (10.5)	<0.001	2246 (5.0)	18 (12.9)	<0.001

Table 4
Univariate and multivariate analysis. Odds Ratio for renal outcomes.

	Univariate OR	95%CI		P value	Multivariate OR	95%CI		P value
Categorical analysis								
eGFR reduction ≥30% of baseline								
TG <150 mg/dL	1.000				1.000			
TG 150–500 mg/dL	1.181	1.084	1.287	<0.001	1.498	1.309	1.714	<0.001
TG >500 mg/dL	1.263	0.474	3.367	0.640	3.461	0.881	13.593	0.075
ESKD								
TG <150 mg/dL	1.000				1.000			
TG 150–500 mg/dL	1.281	0.781	2.103	0.327	0.521	0.311	0.872	<0.050
TG >500 mg/dL	11.435	1.597	81.852	<0.050	6.476	0.879	47.701	0.067
Composite outcome								
TG <150 mg/dL	1.000				1.000			
TG 150–500 mg/dL	1.182	1.085	1.286	<0.001	1.485	1.300	1.696	<0.001
TG >500 mg/dL	1.246	0.468	3.323	0.660	3.274	0.837	12.811	0.088
Continuous analysis								
eGFR reduction ≥30% of baseline								
TG index (by 50 increment mg/dL)	1.062	1.039	1.086	<0.001	1.037	1.012	1.062	<0.010
ESKD								
TG index (by 50 increment mg/dL)	1.174	1.070	1.289	=0.001	0.929	0.814	1.060	0.277
Composite outcomes								
TG index (by 50 increment mg/dL)	1.063	1.040	1.086	<0.001	1.037	1.012	1.062	<0.010

Abbreviations: eGRF, estimated glomerular filtration rate; ESKD, end-stage kidney disease; TG, triglycerides.

[13]. Although its onset is often asymptomatic once GFR lowers to values below 60 ml/min (i.e. stage 3 or greater) the risk of further progression to ESKD increases significantly [14]. Furthermore, low eGFR *per se* entails a dramatic increase in cardiovascular risk and is regarded as an equivalent of cardiovascular event [15].

HTG has increasingly been shown to be a risk predictor of cardiovascular and renal complication, even beyond LDL-cholesterol level [16]. Accordingly, we have recently reported on the same database an association between HTG and higher cardiovascular and total mortality [17]. While HTG has previously been associated to the presence and severity of CKD in cross sectional studies [18,19], data on the predictive role of TG for CKD onset or progression are contrasting. Thus, Tsuruya *et al.* in a large cohort of subjects from general population found that higher serum TG at baseline were significantly associated with a greater decline in eGFR during the 2-year study period, even after adjustment for confounding factors. This was true independent of the presence of CKD at baseline [18–20]. In a large database of subjects with type 2 diabetes in Italy, Russo *et al.* [13]. reported an independent association

between moderately elevated TGs and low HDL with de novo development of stage 3 CKD, i.e. either a sustained reduction of eGFR below 60 mL/min or new onset of albuminuria over a 4 year time period. More recently, in a 7 years retrospective study in older adults in China, Chen and coworkers reported that the HTG-waist phenotype (a clinical proxy of insulin resistance and the metabolic syndrome) was associated with an almost 30% excess risk of CKD even after adjustment for confounders [21]. On the other hand, in a Dutch study conducted on 512 subjects with advanced CKD (i.e. stage 4 and 5) no association was found between lipids parameters, included TG levels, and progression to ESKD or death [22].

A decline in eGFR smaller than a doubling of serum creatinine has been validated as intermediate, clinically meaningful endpoint and has been associated with the risk of ESKD and mortality. Thus, a large meta-analysis [23] has shown that a 30% reduction in eGFR over 2 years is a valid alternative end point for CKD progression. Our renal endpoints seem therefore to be a reasonable choice given the clinical characteristics of study population with baseline GFR well within normal range and the length of our follow-up. Interestingly, we found that the association between HTG and GFR loss overtime held true, although with the limits of a less powerful statical analysis, when traditional, solid renal endpoint such as ESKD incidence was taken into consideration. Our observations expand on the previously reported association between elevated TGs and cardiovascular and renal events in high-risk subgroups such as type 2 diabetes and extends its to a relatively lower risk cohort of general population. It is worthy to note here, that the unfavorable renal prognostic role of HTG reported here was evident for relatively mild TG elevation, a condition often encountered in clinical practice which is likely multifactorial in its pathogenesis, at variance with the more rarely encountered very high TG phenotypes due to well-known genetic abnormalities.

While our study cannot elucidate pathogenetic mechanisms underlying the reported association between HTG and worse renal outcomes, its findings are consistent with previous reports. Indeed, many animal models and clinical studies suggest that dyslipidemia may contribute to renal damage [24]. In fact, inflammatory and oxidative stress, endothelial dysfunction and activation of the renin–angiotensin system have all been shown to be influenced by changes in lipoprotein composition and in cholesterol distribution among plasma, tissues and cellular organelles especially if promoted by remnant cholesterol and TGs [25–28]. More studies are clearly needed to elucidate pathogenetic mechanisms underlying the association between the hight TG phenotypes and renal damage. Furthermore, it remains to be verified whether pharmacologic interventions aimed at lowering TG levels may favourably impact renal outcome. As a matter of fact, HTG is receiving growing attention as a potential target in patients at residual high cardiovascular risk with several new drugs currently under development [29].

Our study has several strengths as well as some limitations that should be acknowledged. Among the previous, the large sample size and length of follow-up that allowed us to capture a sufficient number of events to find significant differences between groups. It is well known that the definition of HTG is complicated by considerable intra-individual variability in TGs over time. To limit this potential source of bias, we have based our classification of high TG categories on at least two concordant TG measurements taken apart. Furthermore, the inclusion of several covariates allowed us to isolate the effect of the TG grouping on adverse outcomes. Previous studies enrolled patients with a broad range of TG levels and evaluated their effect either continuously, after log transformation, or by comparing dichotomized cut-off points or upper and lower tertiles or quintiles of TG. While these characterizations of TG levels deliver significant evidence of an association with risk, they are of restricted clinical value because they do not match guideline-recognized elevated ranges of TG levels. In contrast, our study focused on a definition of HTG that can be easily implemented in clinical practice to characterize individual risk. About limitations, the present study considered observational laboratory data, so that we cannot be certain that all subjects were in the fasting state at the time of their TG tests. However, it has been suggested that non-fasting TGs are better predictors of increased subsequent risk as they tend to show a stronger association with abnormalities in remnants metabolism [30–32]. Thus, we believe this issue should not have significantly impacted our analyses and results since misclassification of subjects with normal fasting but high post-prandial TG levels would have biased our results toward the null. Based on this reasoning, we believe the excess of renal risk we observed in the high TG groups may even be conservative. Second, all variables in our study (including TG levels) were assessed only at baseline. Again, we cannot ensure that changes in lipid parameters as well as in pharmacological treatments during follow-up may have affected our results. Nonetheless, we believe the size of our study cohort and the robustness of our findings allow us to draw intriguing conclusions to be applied to clinical practice. Finally, the number of subjects was smaller and the number of TG measurements was, on average, also smaller in the very high TG group as compared to other groups. However, the relationship we observed between TG values and renal outcomes was consistent across TG categories and proved to be independent of several clinical variables even by linear regression analysis.

In conclusion, we found that moderate-to-severe elevation of TGs is associated with a significant, stepwise increased risk of renal function deterioration as well as ESKD overtime in a large cohort of individuals followed in a real-world clinical setting.

Funding

Alfasigma (Italy) purchased the study report that is the basis for this article. The views expressed here are those of the authors and not necessarily those of the supporters. Alfasigma did not influence the conduction of the project, the discussion of results, and the decision to submit the manuscript to this journal.

Declaration of Competing Interest

R. Pontremoli has served as a consultant for and has received lecturing fees from Novartis, MSD, AstraZeneca, Boehringer-Ingelheim, Lilly, Novonordisk and Alfasigma.

G. Desideri has received research grant support from AstraZeneca and Menarini; has served as a consultant for Servier, Menarini, FIRMA, and Alfasigma; and received lecturing fees from Servier, Bayer, Guidotti, Bristol Myers Squibb, DOC, and Alfasigma

M. Arca has received research grant support from Aegerion, Amgen, IONIS, Akcea Therapeutics, Pfizer, Regeneron, and Sanofi; has served as a consultant for Amgen, Aegerion, Akcea Therapeutics, Regeneron, Sanofi, and Alfasigma; and received lecturing fees from Amgen, Aegerion, Merck, Pfizer, Sanofi, and Alfasigma.

P.L. Temporelli has received lecturing and consulting fees from Alfasigma; consulting fees from Bayer; lecturing fees from Menarini, MSD, and Servier.

C. Borghi has received research grant support from Menarini Corporate and Novartis Pharma; has served as a consultant for Novartis Pharma, Alfasigma, Grunenthal, Menarini Corporate, and Laboratoires Servier; and received lecturing fees from Laboratoires Servier, Takeda, Astellas, Teijin, Novartis Pharma, Berlin Chemie, and Sanofi.

The agreement signed by CliCon s.r.l. and Alfasigma does not create any entity, joint venture or any other similar relationship between the parties. CliCon s.r.l. is an independent company. Neither CliCon s.r.l. nor any of their representatives are employees of Alfasigma for any purpose. The remaining authors have no disclosures to report.

Acknowledgments

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