Arteriosclerosis, Thrombosis, and Vascular Biology

ORIGINAL RESEARCH

Contemporary Management of Familial and Multifactorial Chylomicronemia Syndromes in Italy: Insights From the National Lipigen Registry

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BACKGROUND: We aimed to compare the molecular and clinical characteristics of patients identified in Italy as affected by either familial chylomicronemia syndrome (FCS) or multifactorial chylomicronemia syndrome (MCS) and to assess the overall benefit of novel triglyceride-lowering therapies prescribed to these patients within the routine clinical care.

METHODS: From the national LIPIGEN-sHTG (Lipid Transport Disorders Italian Genetic Network—Severe Hypertriglyceridemia) registry, 169 patients (57 FCS, 51 MCS, 61 variant-negative, variant-negative MCS) were retrospectively analyzed. Data on clinical and genetic characteristics, medical history, and medications were collected. Peak triglyceride levels were used to define untreated lipid phenotypes.

RESULTS: In FCS, 72% exhibited biallelic *LPL* and 28% *non-LPL* variants; in MCS, 38% (n=19) carried *LPL* variants, and 38% (n=19) carried *APOA5* variants, whereas the remaining individuals were carriers of *LMF1* (n=3), *GPIHBP1* (n=2), and *CREB3L3* or *GPD1* variants (n=8), respectively. Peak TGs were highest in FCS (3000 mg/dL [interquartile range, 2116.0–4265.0]), followed by MCS (1817 mg/dL [interquartile range, 1370.0–3062.0]) and variant-negative MCS (1340.0 mg/dL [interquartile range, 946.5–2508.5]; $P<0.001$). FCS showed a 3.4-fold higher risk of acute pancreatitis than others, whereas no significant differences were observed between groups in the prevalence of atherosclerotic cardiovascular diseases. In the subset of patients with FCS receiving novel therapies (lomitapide or volanesorsen; 35%), triglyceride levels decreased by 62%, as compared with an 11% reduction in those on conventional treatment. Across the cohort, posttreatment triglyceride levels were 895 mg/dL in FCS, 352 mg/dL in MCS, and 386 mg/dL in variant-negative MCS.

CONCLUSIONS: As compared with MCS, patients with FCS showed a more severe phenotype and higher prevalence of *LPL* variants. Lomitapide and volanesorsen provide better triglyceride control, yet only one-third of FCS were treated with these drugs in the routine clinical practice.

Key Words: genetics ■ hypertriglyceridemia ■ lipids ■ pancreatitis ■ triglycerides

Chylomicronemia syndrome (CS) represents a group of lipid disorders characterized by a sustained or transient plasma accumulation of chylomicrons due to impaired lipolytic removal.[1] The clinical hallmark of CS is severe hypertriglyceridemia (sHTG; typically>10 mmol/L), which is associated with an increased risk of acute pancreatitis (AP) and atherosclerotic cardiovascular disease (ASCVD).[2]

CS includes different clinical entities such as familial CS (FCS), multifactorial CS (MCS), and other forms of

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Nonstandard Abbreviations and Acronyms

ALT	alanine aminotransferase
AP	acute pancreatitis
ASCVD	atherosclerotic cardiovascular disease
ASO	antisense oligonucleotide
AST	aspartate aminotransferase
BMI	body mass index
CS	chylomicronemia syndrome
FCS	familial chylomicronemia syndrome
FLD	fatty liver disease
IQR	interquartile range
LPL	lipoprotein lipase
MCS	multifactorial chylomicronemia syndrome
MTP	microsomal triglyceride transfer protein
OR	odds ratio
P/LP	pathogenic/likely pathogenic
sHTG	severe hypertriglyceridemia
SNV	single-nucleotide variant
TRL	triglyceride-rich lipoprotein
vnMCS	variant-negative multifactorial chylomicronemia syndrome

Highlights

- The study confirmed that familial chylomicronemia syndrome and multifactorial chylomicronemia syndrome exhibit distinct genetic architectures, supporting their classification as separate subtypes of severe hypertriglyceridemia with different underlying molecular mechanisms.
- Common single-nucleotide variants, particularly in APO A_5 and LPL (lipoprotein lipase), were found to significantly influence triglyceride levels and clinical severity in patients without rare pathogenic mutations, suggesting a cumulative genetic burden even in so-called polygenic or variant-negative cases.
- Real-world data demonstrated that innovative triglyceride-lowering therapies, such as volanesorsen and lomitapide, are effective in patients with familial chylomicronemia syndrome, yet remain underutilized, highlighting the need for broader clinical adoption to improve disease management.

nongenetically classified sHTG.[3] FCS is a rare autosomal recessive disorder, with an estimated prevalence ranging from 1 in 100 000 to 1 in 1 000 000, caused by biallelic pathogenic variants in genes encoding *LPL* (lipoprotein lipase), the main lipolytic enzyme, as well as its cofactors (*APOC2, APOA5, LMF1,* and *GPIHBP1*).[3] This underlies a severely impaired ability to hydrolyze triglycerides in TRLs (triglyceride-rich lipoproteins) and, therefore, patients with FCS show extreme elevations of plasma triglyceride and markedly increased risk of recurrent AP.[4] In contrast, the more common MCS, with an estimated prevalence of 1 in 600 individuals, is associated with the presence of single-copy variants in candidate genes or an enrichment of common triglyceride-raising single-nucleotide variants (SNVs), whose pathogenic effects are amplified by secondary factors such as insulin resistance, visceral obesity, and diabetes.[4,5] Triglyceride plasma levels in patients with MCS are much more variable, and although under specific circumstances can reach severely elevated values, generally remain in the moderate-high range (triglyceride usually between 3 and 10 mmol/L).[3] In comparison to FCS, MCS is thought to be associated with a more elevated risk of ASCVD.[5,6] A group of MCS do not show gene variants (variant-negative MCS, vnMCS) and is believed to have an increased burden of dysmetabolic conditions such as diabetes, obesity, and metabolic syndrome.[5]

In recent years, several studies have compared the characteristics of FCS and MCS, reporting different results either in terms of the underlying genetic architecture or the risk of associated complications, namely ASCVD.[6–11] Moreover, these previous reports paid less attention to other potential CS-associated complications, such as hepatic steatosis and renal impairment.[12–14] These considerations support the usefulness of additional information to broaden knowledge of the clinical and genetic landscape of CS and the genotype–phenotype correlations, particularly in MCS.

A relevant difference among CS is represented by the response to treatments. While FCS is resistant to conventional triglyceride-lowering therapies such as fibrates and omega-3 fatty acids, so that some patients require plasma exchange,[6] MCS exhibits a more variable response to drugs, including statins.[6] In recent years, interest in developing new treatments has significantly increased, especially for the more severe forms of CS.[15] In Italy, 2 drugs have been approved for FCS: volanesorsen, an antisense oligonucleotide targeting apo CIII, and lomitapide, a small molecule acting as an inhibitor of MTP (microsomal triglyceride transfer protein).[16–22] Clinical trials have demonstrated that both drugs are effective in reducing triglycerides in FCS, although side effects may occur. Indeed, the use of volanesorsen has been associated with thrombocytopenia and that of lomitapide with increased liver fat accumulation. However, these side effects have been considered tolerable, and the overall benefit has been deemed to outweigh the associated risks.[23–25] It must be noted that volanesorsen significantly reduces the risk of AP.[26,27] Nevertheless, their utilization in clinical practice and their impact on triglyceride control remain poorly documented.

The LIPIGEN-sHTG (Lipid Transport Disorders Italian Genetic Network–Severe Hypertriglyceridemia) is a recently established, multicenter, nationwide, observational registry where clinical, biochemical, molecular, and therapeutic information from Italian patients with sHTG are collected, both retrospectively and prospectively. The

present analysis of the LIPIGEN-sHTG data is aimed at (1) describing the genetic architecture of FCS and MCS in Italy; (2) presenting the clinical and biochemical characteristics of Italian patients affected by FCS and MCS; (3) assessing the use and the effectiveness of pharmacological treatments, with a special focus on novel triglyceride-lowering drugs.

MATERIALS AND METHODS

Reporting and Data Availability

This study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for observational research. The completed Strengthening the Reporting of Observational Studies in Epidemiology checklist is provided as Supplemental Material.

The data underlying this article cannot be shared publicly due to privacy concerns for individuals who participated in the study. A selected portion may be shared on reasonable request to the corresponding author.

Patients' Selection, Data Collection, and Definition

LIPIGEN is an ongoing, multicenter, nationwide, observational registry centered on genetic dyslipidemias, and its protocol has been reported in detail elsewhere.[28] LIPIGEN was approved by the institutional review board of IRCSS MultiMedica (approval code CE/CE/130/2015/LDC) and by the institutional review boards of all participating centers. Written informed consent was obtained from all participants.

Lipid clinics within the LIPIGEN network (Figure 1A) were invited to contribute data on patients with nonsecondary sHTG who had undergone a genetic test. The selection of patients was not based on prespecified triglyceride cutoff levels, and the decision to perform a genetic test was made at the discretion of the referring clinician mainly based on the presence of refractory HTG. Therefore, molecular testing occurred at variable time points during follow-up. Moreover, often patient's data were entered into the LIPIGEN-sHTG registry after initiation of triglyceride-lowering therapy with substantial heterogeneity in treatment duration and intensity. The final cohort considered for the present analysis comprised 169 patients genetically tested for sHTG and with comprehensive clinical and laboratory data (Figure 1B).

At the time of enrollment in the registry (the entry visit), clinical, genetic, biochemical, and pharmacological data were recorded. Lipid values corresponding to the highest triglyceride levels documented in the patient's history were extracted to define the peak lipid profile. This profile was then used to characterize the lipid phenotypes of the patients. As part of the analysis, the lowest triglyceride values recorded during follow-up were also collected for each patient and defined as the lowest or nadir triglyceride levels. These values were used to further characterize the response to therapy across genetic

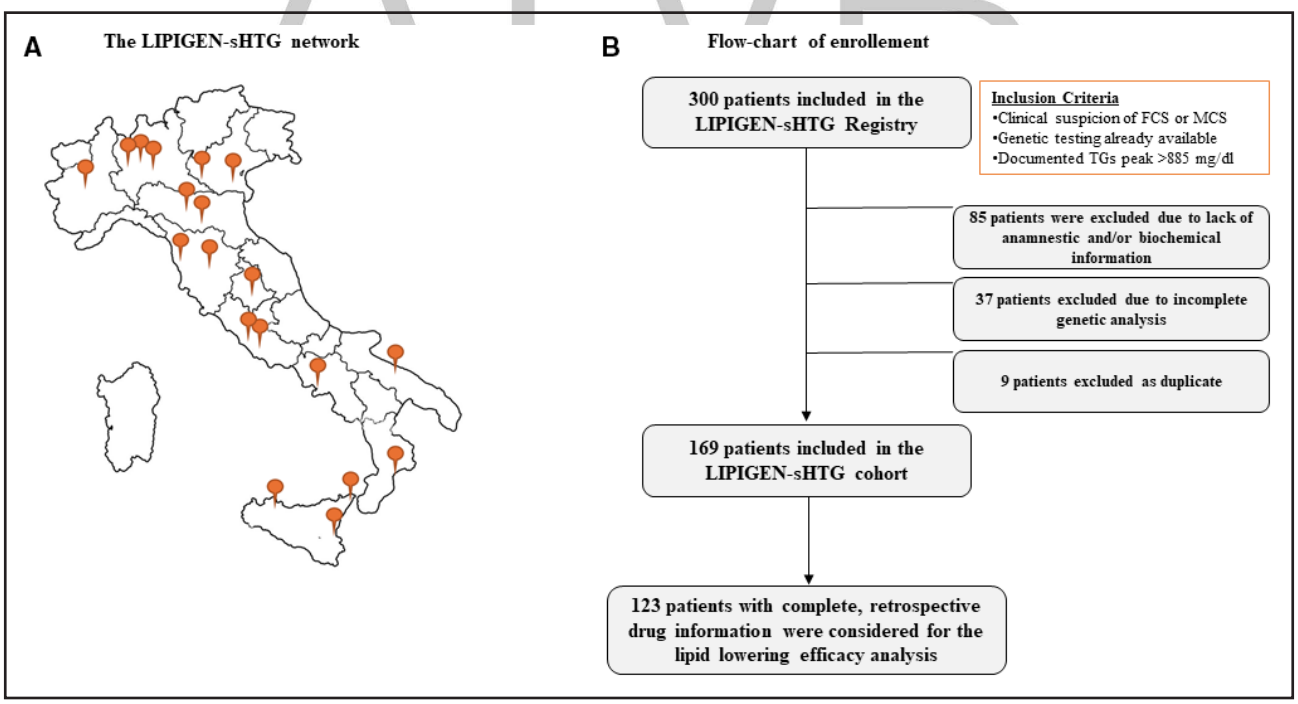

Figure 1. This figure illustrates the process of constructing the patient cohort for the study on severe hypertriglyceridemia (sHTG).

The figure provides the distribution of patients across the LIPIGEN network and a step-by-step breakdown of the selection criteria. **A**, The geographic distribution of Lipid Clinics within the LIPIGEN-sHTG (Lipid Transport Disorders Italian Genetic Network–Severe Hypertriglyceridemia) network. Each point represents the location of a Lipid Clinic in the Italian territory. **B**, Flowchart of patient enrollment in the LIPIGEN-sHTG study. A total of 300 patients with triglyceride (TG) ≥500 mg/dL and complete genetic testing for familial chylomicronemia syndrome (FCS)/multifactorial chylomicronemia syndrome (MCS) were enrolled; 131 were excluded due to missing clinical, biochemical, or genetic data, or because they were duplicate entries. In total, 169 patients were included in the final analysis of this study. Of the 169 patients, 123 had retrospective data available on plasma lipids and TG-lowering therapies from their first visit at the Lipid Clinic.

subgroups. Clinical information included the history of type 2 diabetes, hypertension, obesity, and chronic kidney disease, defined by standard criteria. Estimated glomerular filtration rate was calculated using the CKD-EPI formula.[29] Self-reported history of AP, chronic pancreatitis, and ASCVD was also collected. ASCVD was defined as a composite of coronary, cerebrovascular accident, and peripheral vascular disease, including revascularization procedures (selective or not) and abdominal aortic aneurysms. All outcomes were reported by treating physicians without independent adjudication. Liver ultrasound performed closest to the entry visit was retrieved to assess fatty liver disease (FLD), classified qualitatively as mild, moderate, moderate-severe, or severe.[30,31]

Participating centers were also asked to provide retrospective data on lipid levels and treatments at the patient's initial lipid clinic evaluation. For 46 patients, the entry visit coincided with their first clinic visit. A subgroup of 123 patients was included in a retrospective analysis assessing changes in lipid-lowering therapy and lipid profiles over time.

Genetic Analysis

Genetic analyses were performed at each site in accordance with local protocols. Both Sanger sequencing (43 samples, 25%) and Next Generation Sequencing technologies (126 samples, 75%) were used to sequence the coding regions of candidate genes, including *LPL, APOA5, APOC2, LMF1,* and *GPIHBP1.* For samples analyzed with Next Generation Sequencing, additional triglyceride-raising noncanonical genes, such as *GPD1* and *CREB3L3*, were also sequenced. The raw genetic data were analyzed locally using in-house pipelines with the hg19 human genome as a reference. Subsequently, the data were transmitted to the coordinating LIPIGEN center, where variant annotation and pathogenicity classification were centrally performed by ADC using Varsome Premium (version 11.17.0) and following ACMG guidelines.[32] In instances of uncertainty, the final classification was determined with clinical input from MA and LD.

Patients with rare biallelic pathogenic/likely pathogenic (P/LP) variants in any of the 5 canonical genes were classified as having FCS. Patients with P/LP variants or rare variants of uncertain significance in the heterozygous state were classified as MCS. Patients carrying only common small-effect SNVs, such as *APOA5* c.-3A>G (rs651821), c.56C>G (p.S19W, rs3135506), c.457G>A (rs3135507) in *APOA5*, and c. 106G>A (p.D36N, rs1801177) or c.953A>G (p.N318S, rs268) in *LPL*, or benign variants in other genes (*LMF1, GPD1*), or lacking any detectable variants were classified as having vnMCS. As the genetic screening mostly included only canonical HTG genes, it was impossible to generate in this cohort a complete triglyceride polygenic risk score.

Statistical Analysis

Continuous variables were presented as means and SD for normally distributed data, or medians and interquartile ranges (IQRs) for skewed data. Categorical variables were summarized as frequencies and percentages. Comparative analyses were conducted using the χ^2 test for categorical variables and the ANOVA or Kruskal-Wallis tests for continuous variables, as appropriate. The total number of AP events was calculated by aggregating the individual event counts. The overall number of pancreatic events was estimated by aggregating the number of patients with AP and chronic pancreatitis events. The paired *t* test and McNemar test were used for the assessment of over-time changes in plasma lipids and triglyceride-lowering therapies, respectively.

Multivariate logistic regression analyses with stepwise approaches were used to identify independent factors associated with AP, CVD, and FLD, whereas multivariate linear regression analysis was used to estimate factors associated with triglyceride levels. Results were expressed as odds ratios (ORs) with 95% CIs and standardized β coefficients with 95% CIs, respectively. The models were adjusted for multiple confounders that were selected based on clinical relevance or statistical significance ($P<0.05$) in univariate analyses.

For the statistical comparisons, a 2-tailed $P\leq0.05$ was considered significant. All statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) version 25.0 (IBM Corp, Armonk, NY).

RESULTS

Genetic Profile of Study Patients

Among the 169 enrolled patients, 57 (33.7%) were molecularly diagnosed as FCS, whereas the remaining 112 (66.3%) as either MCS (n=51, 30.2%) or vnMCS (n=61, 36.1%). Among FCS, 72% of patients had rare, biallelic P/LP variants in the *LPL* gene, whereas 28% (n=16) had biallelic P/LP variants in *non-LPL* genes. Among these, the majority were homozygotes for *APOA5* variants (8.8%; n=5), followed by *APOC2* (7.0%; n=4), homozygotes and compound heterozygotes for *GPIHBP1* (7.0%; n=4 and 3.5%; n=2, respectively) and homozygotes for *LMF1* (1.8%; n=1; Figure 2A). Among MCS, 38% of patients (n=19) were carriers of variants in *APOA5*, 38% (n=19) of variants in *LPL*, whereas variants in *CREB3L3* or *GPD1* were detected in 15.6% of patients (n=6 in *CREB3L3* and n=2 in *GPD1*). Three patients with MCS were identified as heterozygous carriers of a pathogenic variant in *LMF1* and 2 in *GPIHBP1* (Figure 2B). Among vnMCS, most patients (n=25, 41%) were carriers of the SNV in the *APOA5* gene (ie, p.S19W, either at homozygous or heterozygous state) and 12 (19.6%) were carriers of the p.D36N and p.N318S SNVs in the *LPL* gene. Fourteen patients (23%) did not show variants in any screened genes. Finally, 10 (16.3%) of patients were positive for other SNVs (see Materials and Methods for specifications).

Table S1 contains the list of the unique pathogenic and likely pathogenic variants identified. Most of them were already reported in literature, whereas 11 were novel.[6,33–36] Overall, 194 genetic variants were detected, and almost half were located in the *LPL* gene (47%, n=91). Most variants were missense (72.4%), with a distribution of 52.3% in FCS and 82.7% in MCS. Nonsense

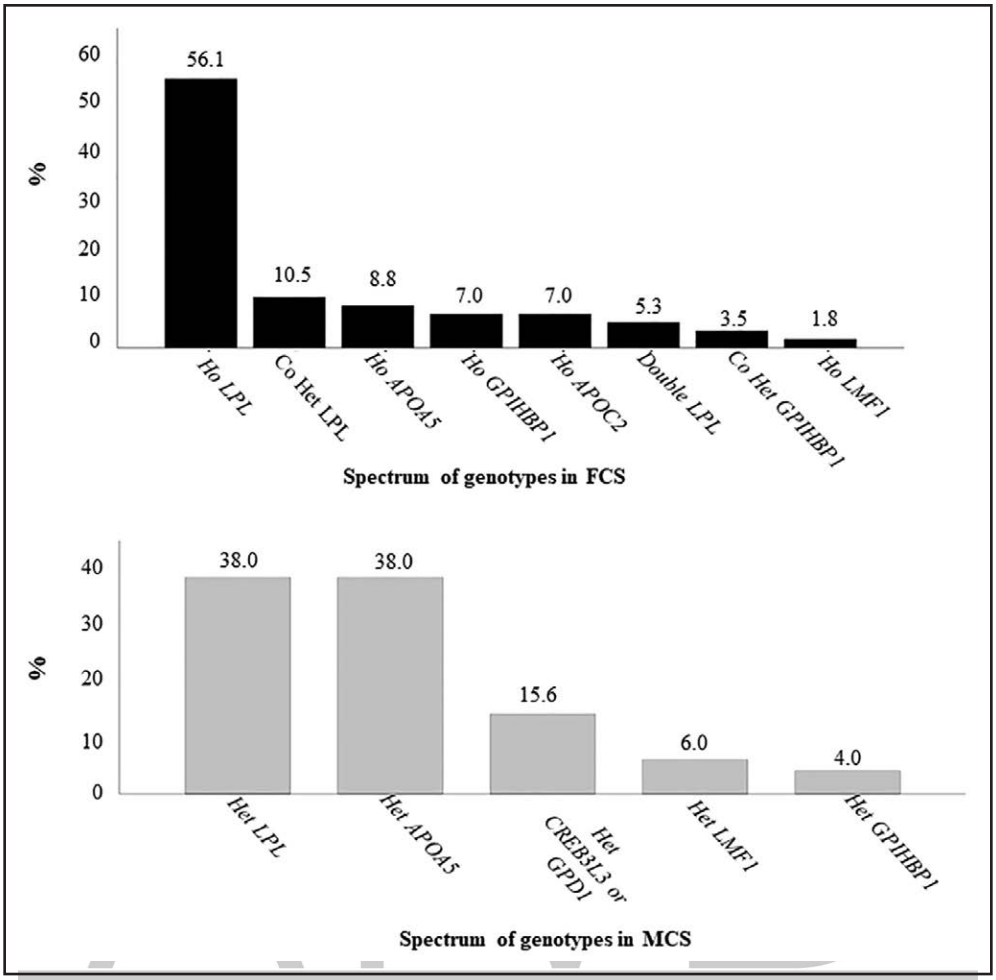

Figure 2. Distribution of genotypes in patients with familial chylomicronemia syndrome (FCS) and multifactorial chylomicronemia syndrome (MCS) enrolled in the LIPIGEN-sHTG study (Lipid Transport Disorders Italian Genetic Network–Severe Hypertriglyceridemia).

This figure shows the genetic characteristics of patients enrolled in the LIPIGEN-sHTG study. **A** shows the spectrum of genotypes in FCS cohorts, whereas **B** shows the spectrum of genotypes in MCS cohorts according to the tested genes. He indicates heterozygous; Ho, homozygous; LPL, lipoprotein lipase; and non-LPL, nonlipoprotein lipase.

variants followed at a frequency of 16.5% (24.6% in FCS and 11.8% in MCS), whereas insertion/deletion (ins/del) variants represented only 6.2% (10.8% in FCS and 3.9% in MCS). Ninety-six variants (50%) were unique, and 67 of them (70%) were classified as P/LP.

Clinical Characteristics of Study Patients

The comparison of clinical characteristics of patients classified as FCS, MCS, and vnMCS at entry visit is presented in Table 1. In all groups, patients were mainly of White origin, males, and middle-aged. Unlike patients with FCS, those with MCS and vnMCS were overweight. The FCS group also exhibited a lower prevalence of smoking habits. No difference in the history of hypertension, diabetes, and chronic kidney disease was noted among groups. Additionally, no significant differences in estimated glomerular filtration rate were found. Plasma glucose level was higher in the MCS group than in the FCS group, whereas liver transaminase levels were comparable.

As compared with MCS and vnMCS, patients with FCS exhibited a worse lipid profile (Table 1). In particular, the median peak triglyceride level was 3000.0 mg/dL (IQR, 2116.0–4265.0 mg/dL) in FCS, 1817.0 mg/dL (IQR, 1370.0–3062.0 mg/dL) in MCS, and 1340.0 mg/dL (IQR, 946.5–2508.5 mg/dL) in vnMCS ($P<0.001$). At the entry visit, triglyceride levels remained highest in the FCS group (859.0 mg/dL [IQR, 494.5–1642.5 mg/dL]), whereas patients with vnMCS showed slightly higher values (466.0 mg/dL [IQR, 216.5–1076.5 mg/dL]) than those with MCS (363.0 mg/dL [IQR, 200.0–815.0 mg/dL]; $P<0.001$; Table 1). Median total cholesterol and high-density lipoprotein cholesterol (HDL-C) levels were significantly lower in the FCS group than in the other groups (Table 1). Meanwhile, the median non–HDL-C was lower, albeit not statistically significant, in FCS subjects (Table 1).

Table 1. Clinical Characteristics of Enrolled Patients at Entry Visit Stratified by Genotypes

	FCS (n=57)	MCS (n=51)	vnMCS (n=61)	*P* value
Age, y, mean±SD	44.2±19.0	45.7±15.7	41.1±13.2	0.31
Males, n (%)	28 (49.1)	27 (52.9)	39 (63.9)	0.24
Race (White), n (%)	55 (96.5)	46 (90.2)	60 (98.4)	0.11
Age at molecular diagnosis, y, mean±SD	36.3±20.7	41.9±17.9	41.6±12.2	0.27
Smokers, n.(%)	14.0	34.2	36.8	0.040
BMI, kg/m^2, mean±SD	22.8±4.3	27.7±5	29.6±4.8	<0.001
Hypertension, n (%)	17 (30.4)	19 (37.3)	19 (31.1)	0.70
Diabetes, n (%)	11 (19.3)	14 (27.5)	15 (24.6)	0.59
CKD history, n (%)	3 (5.3)	5 (9.8)	4 (6.6)	0.64
Peak plasma lipids, mg/dL, median (IQR)				
TG	3000.0 (2116.0–4265.0)	1817.0 (1370.0–3062.0)	1340.0 (946.5–2508.5)	<0.001
TC	306.5 (220.2–413.2)	287.0 (226.2–493.0)	278.0 (206.386.5)	0.45
HDL-C	18.0 (12.0–30.5)	24.0 (19.0–32.5)	29.0 (23.5–41.7)	<0.001
Lowest plasma lipids, mg/dL, median (IQR)				
TG	372.5 (132.5–616.2)	190.0 (138.0–329.0)	231.0 (134.5–365.5)	0.06
TC	128.0 (76.7–163.5)	166.5 (135.0–204.5)	159.0 (128.0–201.0)	<0.001
HDL-C	22.0 (16.7–29.0)	35.0 (27.5–39.5)	37.0 (28.0–47.0)	<0.001
Plasma lipids at entry visit, mg/dL, median (IQR)				
TG	859.0 (494.5.0–1642.5)	363.0 (200.0–815.0)	466.0 (216.5–1076.5)	<0.001
TC	168.5 (123.0–231.7)	198.0 (152.0–242.0)	199.0 (171.5–281.2)	0.013
HDL-C	18.0 (15.0–23.0)	30.0 (23.0–38.0)	35.0 (26.0–47.0)	<0.001
Non–HDL-C	143.0 (102.0–182.0)	161.0 (121.0–204.0)	162.0 (128.0–191.0)	0.55
Biochemistry at entry visit, median (IQR)				
Fasting glucose, mg/dL	87.0 (80.0–102.0)	102.0 (88.0–117.0)	94.5 (82.0–104.0)	0.049
Creatinine, mg/dL	0.76 (0.60–0.93)*	0.84 (0.71–1.02)†	0.8 (0.68–1.0)‡	0.14
eGFR, mL/min^2	104.0 (84.5–114.5)*	91.0 (62.3–104.5)†	102.2 (72.3–111.0)‡	0.09
AST, U/l	27.5 (18.7–36.2)	26.0 (20.0–31.0)	24.0 (16.0–33.0)	0.59
ALT, U/l	22.0 (13.0–33.0)	26.0 (20.0–31.0)	26.0 (19.2–35.0)	0.63
Lipid-lowering therapies at entry, n (%)				
Fibrates	43 (78.2)	34 (68.0)	34 (55.7)	0.03
Omega-3 fatty acids	49 (89.1)	32 (62.7)	33 (55.0)	<0.001
Statins	8 (14.5)	10 (19.6)	15 (24.6)	0.39
Ezetimibe	2 (3.6)	7 (13.7)	11 (18.0)	0.053
MCT oil	18 (32.7)	2 (3.9)	5 (8.2)	<0.001
Apheresis	3 (5.5)	2 (3.9)	0	0.20
Novel therapies	20 (35.1)	3 (5.8)	0	<0.001
Volanesorsen	11 (20.0)	2 (3.9)	0	<0.001
Lomitapide	9 (16.4)	1 (2.0)	0	<0.001

The demographic, clinical, biochemical, and therapeutic characteristics are presented as median (IQR), mean±SD, or number (percentage), as appropriate. The information is reported according to genotype, as detailed in the Materials and Methods section. Statistical significance for comparisons across the 3 genotype-defined groups (FCS, MCS, and vnMCS) was assessed using 1-way ANOVA for normally distributed continuous variables and the Kruskal-Wallis test for non-normally distributed ones (as assessed by the Kolmogorov-Smirnov test). Categorical variables were compared using the χ^2 test. A $P<0.05$ was considered statistically significant. ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FCS, familial chylomicronemia syndrome; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; MCS, multifactorial chylomicronemia syndrome; MCT, medium-chain triglycerides; TC, total cholesterol; TG, triglycerides; V0, visit 0; V1, visit 1; and vnMCS, variant-negative MCS.

*20 missing data.

†19 missing data.

‡26 missing data.

Furthermore, the analysis of the lowest triglyceride values achieved during follow-up confirmed significant differences between the groups. Although median triglyceride levels below 500 mg/dL were observed across all groups, patients with FCS had trend towards higher nadir triglyceride concentrations (372.0 mg/dL [IQR, 132.5–616.2 mg/dL]) compared with MCS (190.0 mg/dL [IQR, 138.0–329.0 mg/dL]) and vnMCS (231.0 mg/dL [IQR, 134.5–365.5 mg/dL]) individuals (P=0.06). It is noteworthy that at the nadir of triglyceride, patients with FCS exhibited significantly lower HDL-C levels (22.0 mg/dL [IQR, 16.7–28.0 mg/dL]) compared with MCS (35.0 mg/dL [IQR, 27.5–39.5 mg/dL]) and vnMCS (37.0 mg/dL [IQR, 28.0–47.0 mg/dL]) groups (P<0.001). In addition, total cholesterol levels at nadir appeared lower in FCS (128.0 mg/dL [IQR, 76.7–163.5 mg/dL]) compared with MCS (166.5 mg/dL [IQR, 135.0–204.5 mg/dL]) and vnMCS (159.0 mg/dL [IQR, 128.0–201.0 mg/dL]; P<0.001). At entry visit, fibrates and omega-3 fatty acids were the most frequently used treatments across all genotypes (Table 1). However, although the use of fibrates was comparable between groups, the use of omega-3 fatty acids was more frequent in FCS as compared with the others (P<0.001). Similarly, medium-chain triglyceride oil was almost exclusively prescribed to patients with FCS. Conversely, when comparing patients with MCS and vnMCS with patients with FCS, a higher utilization of ezetimibe (13.7% versus 18.0% versus 3.6%, respectively [P=0.053]) and statins (19.6.5% versus 24.6% versus 14.5%, respectively [P=0.39]) was observed. Five patients (3 FCS and 2 MCS) were receiving plasmapheresis, but information on the frequency of treatments was not available. Twenty-three patients (35% of the FCS cohort, 5.8% of the MCS cohort) were prescribed novel therapies. Most patients (11 in FCS, 2 in MCS) received volanesorsen, whereas 9 in FCS (16.4%) and 1 in MCS received lomitapide (mean dosage 27.0±14.7 mg/d).

Figure 3 shows peak triglyceride profiles stratified by groups and genes. Among patients with FCS, median peak triglyceride was highest in those carrying biallelic *LPL* variants (3312.0 mg/dL [IQR, 2588.5–5010.0 mg/dL]), compared with *non-LPL* carriers overall (1847.5 mg/dL [IQR, 1575.5–2789.0 mg/dL]; P=0.001). Interestingly, within the *non-LPL* group, patients with FCS carrying biallelic pathogenic variants in the *GPIHBP1* gene exhibited the highest triglyceride peak levels (2231.5 mg/dL [IQR, 1682.2–2819.7 mg/dL]; Figure 3A). In the MCS group *GPIHBP1*, *LMF1*, and *APOA5* heterozygous carriers displayed higher peak triglyceride values as compared with *LPL* heterozygotes, which closely overlapped those observed in *CREB3L3* or *GPD1* carriers (Figure 3B). Finally, in the vnMCS group, median triglyceride peaks exceeded 1000 mg/dL across all genotypes. It is noteworthy that patients with common, small-effect SNVs in *APOA5* and *LPL* genes (Figure 3C) showed marked elevation of triglyceride. A more detailed analysis revealed substantial differences among carriers of specific *APOA5* and *LPL* SNVs within the vnMCS group. Interestingly, homozygotes for the *APOA5* p.S19W exhibited a median peak triglyceride of 3758.0 mg/dL (IQR, 2644.5–4380.0 mg/dL), whereas heterozygous carriers of *LPL* p.D36N reached even higher levels, with a median of 4832.0 mg/dL (IQR, 4167.5–5496.5 mg/dL; data not shown).

Clinical Complications

The burden of clinical complications in the study groups is summarized in Figure 4. The prevalence of AP was significantly higher in FCS than in the other groups (61.4% in FCS, 45.1% in MCS, and 29.5% in vnMCS; P=0.002; Figure 4A). Consistently, the number of patients reporting chronic pancreatitis was higher in the FCS group than in the others (23.2% in FCS versus 6.1% in MCS *versus* 5.1% in vnMCS; P=0.004; Figure 4B). A multivariate logistic regression analysis including sex, age, and body mass index

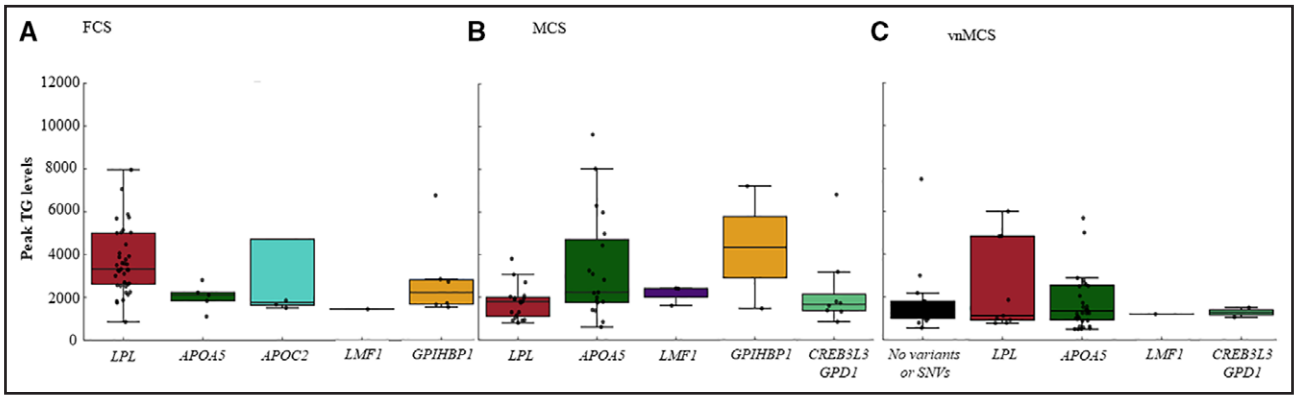

Figure 3. Peak triglyceride (TG)-levels stratified by groups and genes.
The figure shows median and interquartile range (IQR) of TG levels at peak, stratified by genes within each group as follows: (**A**) familial chylomicronemia syndrome (FCS); (**B**) multifactorial chylomicronemia syndrome (MCS); and (**C**) variant-negative MCS (vnMCS). Lines indicate medians; vertical bars represent IQRs.

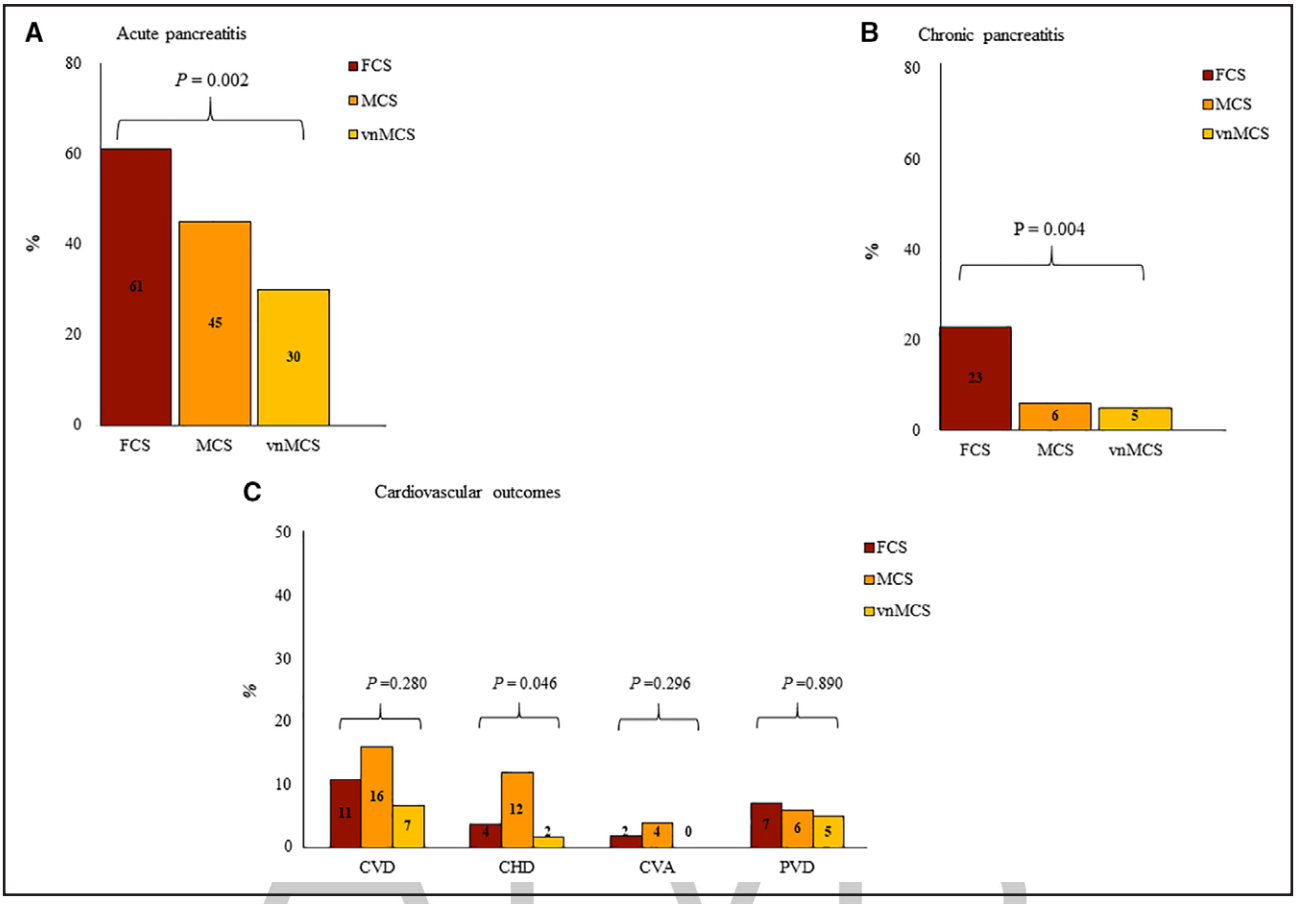

Figure 4. Clinical complications in patients enrolled in the LIPIGEN-sHTG study (Lipid Transport Disorders Italian Genetic Network–Severe Hypertriglyceridemia).
This figure represents clinical outcomes in patients with familial chylomicronemia syndrome (FCS), multifactorial chylomicronemia syndrome (MCS), and variant-negative MCS (vnMCS), enrolled in the LIPIGEN-sHTG study. Data are reported as percentage. Statistical significance was assessed using the χ^2 test. A $P<0.05$ is considered statistically significant and is shown in the figure only when significance is reached. **A**, Prevalence of acute pancreatitis. **B**, Prevalence of chronic pancreatitis. **C**, Prevalence of atherosclerotic cardiovascular disease (CVD) outcomes. CHD indicates coronary heart disease; CVA, cerebrovascular accident; and PVD, peripheral vascular disease.

(BMI) at enrollment, as well as the genetic diagnosis, was performed to identify independent predictors of AP. In this model, age (OR, 1.03 per year [95% CI, 1.003–1.054]; *P*=0.027) and genetically confirmed FCS (OR, 6.61 [95% CI, 2.18–20.04]; *P*=0.001) were significantly associated with an increased risk of AP (data not shown).

Despite the absence of a significant difference across groups in the overall occurrence of ASCVD (10.7% in FCS, 16% in MCS and 6.6% in vnMCS, *P*=0.28; Figure 4C), patients with MCS exhibited a significantly higher prevalence of coronary heart disease compared with both FCS and vnMCS (11.8% versus 3.6% and 1.6%, respectively; *P*=0.046); 1 FCS patient with coronary heart disease also had cerebrovascular accident (both ischemic and hemorrhagic). Patients with FCS showed a trend toward a higher prevalence of peripheral vascular disease compared with others (7.0% in FCS *versus* 6.0% in MCS versus 4.9% in vnMCS). Notably, all patients with FCS with peripheral artery disease showed an abdominal aortic aneurysm. The multivariate model including age, sex, BMI, diabetes, hypertension, non–HDL-C, smoking and genetic diagnosis as covariates, showed that hypertension (OR, 6.45 [95% CI, 1.05–39.4]; *P*=0.044) and age (OR, 1.08 [95% CI, 1.01–1.16]; *P*=0.025) were significantly and independently associated with the risk of ASCVD (data not shown).

As reported in Figure S1A and S1B, FLD (qualitatively categorized as mild, moderate, moderate-severe, and severe) was highly prevalent in the entire CS cohort, although no significant differences were found between the genotypes. Among patients with FCS, at the time of enrollment, levels of AST (aspartate aminotransferase) and ALT (alanine aminotransferase) were higher in patients receiving lomitapide (ALT: 30 U/L [IQR, 12.5–39.5 U/L]; AST: 33.0 U/L [IQR: 20.5–51.5 U/L]) and volanesorsen (ALT: 26.5 U/L [IQR: 20.5–33.7 U/L]; AST: 32.5 U/L [IQR, 25.7–42.0 U/L]). These levels were higher than those observed in patients with FCS not taking these medications (AST: 24 U/L [IQR, 17–31

U/L]; ALT: 19.5 U/L [IQR, 12.2–28.7 U/L]). To identify the factors associated with the presence of FLD, a multivariate logistic regression model was applied. This model included genotypes, diabetes, BMI, age, sex, and the current use of novel therapies. This analysis revealed that age (OR, 1.049 [95% CI, 1.007–1.093]; *P*=0.022) and BMI (OR, 1.318 [95% CI, 1.14–1.53]; *P*<0.001) were independently associated with FLD (data not shown).

A further analysis of the prevalence of clinical conditions by genetic background is presented in Figure S2. AP appeared to be most frequently associated with *APOC2* and *LPL* variants in the FCS group, and with *LMF1* and *APOA5* variants in the MCS group. In contrast, the highest prevalence of ASCVD was observed in patients with MCS carrying *LMF1*, *CREB3L3*, or *GPD1* variants. Among patients with vnMCS, AP was more common in patients without detectable pathogenic variants, whereas ASCVD prevalence was similar in patients with or without detected variants.

Response to Lipid-Lowering Therapies

In a subgroup of 123 patients (51 FCS, 38 MCS, and 34 vnMCS), we were able to retrospectively report changes in lipid-lowering therapy as well as in lipid levels over time (Table 2). It is important to note that the length of the follow-up period differed between groups, with FCS having a longer follow-up period than patients with MCS or vnMCS (8.3±7.2 versus 3.3±4.2 versus 3.5±4.1 years, respectively; *P*<0.001). Table 2 illustrates the progressive intensification of lipid-lowering therapy during follow-up, which was characterized by larger utilization of fibrates and omega-3 fatty acids alongside the use of novel agents. The number of patients with FCS undergoing plasmapheresis did not change during follow-up. Although the use of novel therapies is recommended only for patients with FCS, 3 patients with MSC received these drugs.

The intensification of lipid-lowering therapies during follow-up was paralleled by a significant improvement in triglyceride control in all groups. Plasma triglyceride levels decreased by 37.3% (IQR, −67.1% to 32.6%; *PpairedTtest*=0.005) in patients with FCS, by 61.7% (IQR, −84.1% to 18.8%; *PpairedTtest*=0.19) in patients with MCS, and by 55.8% (IQR, −22.4% to −79.7%; *PpairedTtest*<0.001) in patients with vnMCS (Table 2; *Pfor trend*=0.19). The benefit of novel therapies was assessed in a subanalysis by comparing the lipid profile in the group of FCS receiving novel therapies as add-on versus conventional therapies alone. The first group experienced a median triglyceride change of −62.0% (IQR, −75.6% to −40.7%), significantly >−10.8% (IQR, −59.3% to

Table 2. Changes in Lipid-Lowering Therapies and Lipid Values During Follow-Up in the Study Patients

	FCS (n=51)			MCS (n=38)			vnMCS (n=34)		
	First	Entry	*P* value	First	Entry	*P* value	First	Entry	*P* value
Follow-up, y, mean±SD	8.3±7.2		…	3.3±4.2		…	3.5±4.1		<0.001
Plasma lipids, mg/dL, median (IQR)									
TC	206 (146–305)	168.5 (123–228)	0.005	245 (176–401)	197 (145–240.5)	0.013	233 (217–311)	196 (164.5–220)	0.006
HDL-C	18 (13–24)	18 (14–23.2)	0.33	30.5 (27–35)	31 (24–39.5)	0.58	33.5 (28–40.2)	36 (26.5–48)	0.27
TG	1670 (856–2700)	895 (526–1686)	0.005	1019 (522–1825)	352 (197–818.2)	0.14	973.5 (611–1816)	386 (164.7–640.5)	<0.001
Δ% TGs	−37.3 [− 67.1 to 32.6]			−61.6 [− 84.0 to 18.8]			−55.7 [−22.4 to −79.7]		0.19
Lipid-lowering therapies, n (%)									
Statins	5 (9.8)	7 (14.3)	0.625	7 (18.4)	8 (21.1)	*P*>0.99	3 (8.8)	12 (35.3)	0,004
Ezetimibe	2 (3.9)	2 (3,9)	*P*>0.99	5 (13.2)	6 (15.8)	*P*>0.99	2 (5.9)	9 (26.5)	0,016
Fibrates	32 (62.7)	39 (79.6)	0.022	15 (39.5)	25 (67.6)	0.003	9 (26.5)	20 (58.8)	0,007
Omega-3 fatty acids	35 (68.6)	49 (96.1)	0.008	14 (36.8)	24 (63.2)	0.002	8 (23.5)	18 (54.5)	0,006
MCT oil	12 (23.5)	14 (28.6)	0.75	1 (2.6)	2 (5.3)	*P*>0.99	0	3 (8.8)	…
Apheresis	7 (13.7)	3 (6,1)	0.219	3 (7.9)	2 (5.3)	*P*>0.99	1 (3)	0	…
Lomitapide	0	9 (17.6)	…	0	1 (2.6)	…	0	0	…
Volanesorsen	0	9 (17.6)	…	0	2 (5.3)	…	0	0	…

This table illustrates changes in the lipid profile over time, categorized by genotype as detailed in the Materials and Methods section. The follow-up period is defined as the duration between V1 (first) and V0 (entry). The percentage change in triglyceride levels (Δ% TGs) is calculated using the following formula: ([TGs at enrollment—TGs at initial visit]/TGs at initial visit)×100. Statistical significance for within-group comparisons of continuous variables between the first and entry visits was assessed using the paired *t* test. Categorical variables were analyzed using the McNemar test. Differences in follow-up duration between genotype groups were assessed using 1-way ANOVA. A *P*<0.05 was considered statistically significant. FCS indicates familial chylomicronemia syndrome; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; MCS, multifactorial chylomicronemia syndrome; MCT, medium-chain triglycerides; TC, total cholesterol; TG, triglycerides; and vnMCS, variant-negative MCS.

85.7%) observed in the second group (*P*=0.009; Figure 5A). This corresponded to an absolute triglyceride reduction of −1255.5 mg/dL (IQR, −2093.5 to −609.0 mg/dL) with novel drugs, compared with −91.0 mg/dL (IQR, −953.0 to 772.0 mg/dL) with conventional therapies (*P*=0.005; Figure 5B). Consequently, at the time of data capture, triglyceride levels were lower in patients with FCS receiving novel therapies (median, 708.0 mg/dL [IQR, 503.7–1176.2 mg/dL]) as compared with those receiving conventional therapies (median, 1319.0 mg/dL [IQR, 583–2267.0 mg/dL]), though this difference was of borderline statistical significance (*P*=0.08). The use of volanesorsen and lomitapide provided comparable lipid-lowering effects, as they determined a triglyceride decrease of 65.7% (IQR, 41.8%–67.1%) and 65.2% (IQR, 29.6%–84.4%), respectively. No sex-specific differences in the triglyceride-lowering efficacy of innovative therapies were observed.

DISCUSSION

This study aimed to provide additional information on the genetic architecture and the clinical phenotype of FCS and MCS by describing the molecular, clinical, and biochemical features of patients enrolled in the Italian national LIPIGEN-sHTG registry. A distinctive aspect of the present analysis is the evaluation of the use and effectiveness of novel triglyceride-lowering drugs in routine clinical practice.

Our results confirm that FCS is primarily caused by rare, pathogenic, biallelic variants in the *LPL* gene, which were present in 72% of cases, whereas the remaining one-third was caused by non-*LPL* variants. This finding is consistent with previous studies, where, indeed, the contribution of *non-LPL* genes to the FCS phenotype ranged from 16% to 36%.[6–11] However, it must be highlighted that the genetic architecture of this condition has been reported to be different in non-European populations, where non-*LPL* variants may account for up to 54% of FCS cases.[7] Although most gene variants identified in FCS were already known, the present study also identified novel variants in the *LPL* and *GPIHBP1* genes, further supporting the molecular heterogeneity of this condition. In line with the findings of Hegele et al,[4] patients with *LPL*-related FCS in the LIPIGEN-sHTG cohort exhibited a more severe phenotype than those with *non-LPL* FCS, with peak triglyceride levels of 3312 mg/dL (IQR, 2614–5000 mg/dL) and a history of AP in 70.7% of cases, as compared with 1889.25 mg/dL (IQR, 1654.53–2802.68 mg/dL) and 37.5%, respectively, in the *non-LPL* FCS group. These results confirm that functional rare variants affecting the activity of the key lipolytic enzyme LPL are associated with a higher severity of this disorder. Finally, about half of patients with FCS were true homozygotes for 20 distinct unique *LPL* variants, a pattern comparable with other reports and reflecting a degree of genetic heterogeneity in the inheritance of this rare lipid disorder.

The genetic architecture of patients with MCS deserves further consideration. In our cohort, 38% of these patients carried heterozygous rare variants in *APOA5*, which contrasts with the results reported by Bashir et al,[7] where this prevalence was only 23%. However, it must be recognized that Bashir's cohort showed a higher prevalence of non-European ethnicities, whereas most patients in our cohort were White. Finally, a small but significant proportion of patients with MCS (11%) were positive for rare P/LP variants in the noncanonical *CREB3L3* gene, which contributed more to the MCS phenotype than the other 2 canonical genes, *GPIHBP1* and *LMF1*. Depending on future research, a case can be made to include *CREB3L3* on sequencing panels for FCS and HTG.

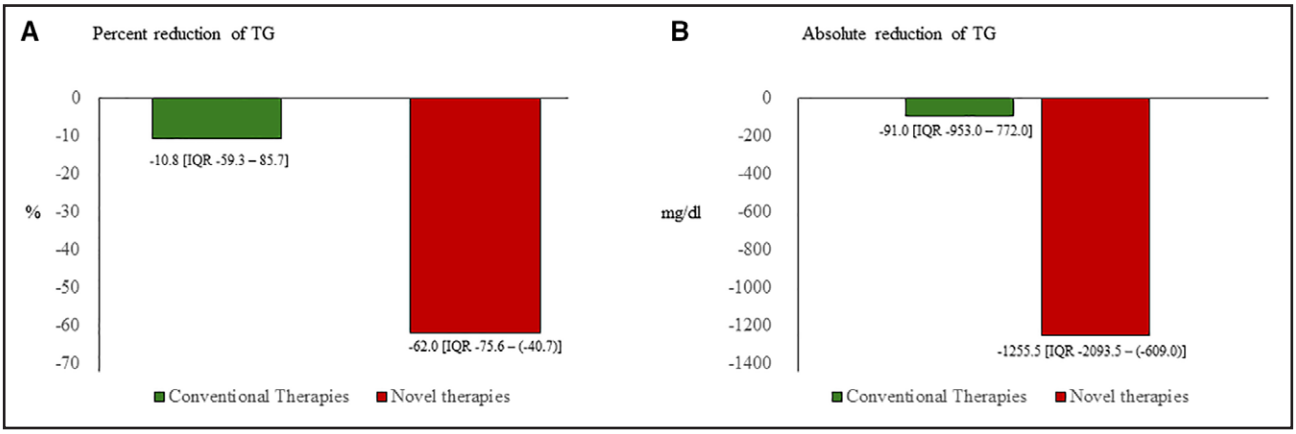

Figure 5. Changes in triglyceride (TG) levels in patients with familial chylomicronemia syndrome according to the type of treatment.

This figure represents changes in TGs that occurred during follow-up according to the type of prescribed therapies (novel vs conventional). The follow-up period is defined as described in Materials and Methods. A *P*<0.05 is considered significant. **A**, The percentage reduction of TG during follow-up. Data are reported as median values. **B**, Absolute reduction of TG during follow-up. Data are reported as median values. IQR indicates interquartile range.

An additional layer of complexity emerged from the analysis of data in the subgroup of patients with vnMCS, who accounted for 35.8% of the study cohort. Although these individuals were negative for rare pathogenic variants in both canonical and noncanonical genes, they still exhibited sHTG, with median triglyceride peaks exceeding 1000 mg/dL, and in some cases exceeding levels typically associated with monogenic FCS. Notably, a subset of patients with vnMCS were carriers of common SNVs previously considered to have modest individual effects on triglyceride levels. However, in our analysis, homozygous carriers of *APOA5* p.S19W and *LPL* p.D36N reached triglyceride peaks of 3758 and 4832 mg/dL, respectively. These values not only exceeded the vnMCS group median peak triglyceride levels, but also approached those observed in patients with FCS. Of note, both genotypes were also associated with markedly elevated triglyceride levels at study entry, suggesting a sustained dysregulation of triglyceride metabolism. It should also be noted that AP was reported in 75% of individuals homozygous for *APOA5* p.S19W and in 66.6% of those heterozygous for *LPL* p.D36N, underscoring a substantial clinical burden associated with these variants. These findings rise 2 key considerations: (1) the genotype–phenotype mismatch may occur even in the absence of rare high-impact variants, suggesting a possible cumulative effect of common and low-penetrance SNVs, especially in the context of adverse metabolic environments (eg, diabetes, obesity, low estimated glomerular filtration rate); (2) the current dichotomous genetic classification triglyceride of sHTG into monogenic or polygenic may not capture or might underestimate the genetic complexity of MCS. However, we were not able to calculate a triglyceride polygenic risk score in vnMCS. A substantial polygenic contribution to HTG in these individuals is highly likely, as suggested by their clinical and biochemical profiles, although it was not directly assessed in the present analysis. Therefore, it remains possible that the severe HTG phenotype seen in these groups might be the consequence of a high burden of undetermined triglyceride-raising SNVs.

The differences in the clinical profiles of FCS versus MCS were less pronounced in our cohort as compared with other cohorts.[6–11] It is possible that this observation is because our patients have already undergone therapeutic interventions aimed at weight reduction or improved glycemic control by the time of enrollment. Unfortunately, detailed information on other, nonlipid-directed therapies was not available, and, therefore, we cannot fully support this hypothesis. Nonetheless, the prevalence of AP and chronic pancreatitis was significantly higher in FCS as compared with patients with MCS, as described in previous investigations.[6–11] In particular, the UK FCS National Registry and the UK arm of the FCS International Quality Improvement and Service Evaluation Project reported a prevalence of AP of 84% in FCS versus 60% in MCS.[7] In the French cohort, 58.6% of patients with FCS experienced at least 1 episode of AP during the follow-up period, in comparison with 19.4% of patients with MCS.[9] These data are similar to those observed in our study, which combined the history of AP with that of chronic pancreatic disease. Overall, this translated into an almost 3.5-fold increased risk of pancreatic complication in FCS as compared with MCS.

Notably, although FCS is traditionally considered to be associated with a lower risk of ASCVD, the present study did not record a significant difference between FCS and MCS. This observation is in partial agreement with the observation of Bashir et al,[7] but in contrast with that of Belhassen et al,[9] who showed that the incidence of ASCVD was higher in patients with MCS. It must be considered that our definition of ASCVD was quite broad, as it also included the presence of peripheral vascular disease. In this regard, it is noteworthy that some patients with FCS reported a history of abdominal aortic aneurysm, incidentally discovered during abdominal ultrasound examinations.

In agreement with other reports,[12,13] we noted that FLD was highly prevalent in the entire cohort, with no difference between FCS and MCS, and BMI was the only associated factor. This suggests that patients with sHTG, regardless of the underlying cause, are at higher risk of FLD. Nevertheless, the relationship between FLD and FCS/MCS requires further systematic studies, which use more accurate methods to quantify liver fat content and to estimate its clinical sequelae, such as hepatic fibrosis and the associated risk of cardiovascular disease.[30] Consequently, no definitive conclusions about hepatic safety can be drawn from this study, and prospective data are needed to clarify this issue.

Fibrates and fish oil showed significant efficacy in patients with MCS, achieving a 60.9% reduction in triglycerides (from 1028 to 386 mg/dL), in contrast to the limited response typically observed in patients with FCS (10% reduction with conventional therapies only). These findings align with the results reported in previous cohorts.[6,7,9] In line with these findings, the lowest triglyceride levels achieved remained significantly higher in FCS than in MCS and vnMCS. This further highlights the limited capacity of current therapies to normalize the lipid profile in this population. It is also important to note that HDL-C levels remained disproportionately low, even at the point when lipids were at their lowest. This suggests that there is a persistent deficit in lipoprotein metabolism, despite the implementation of therapeutic efforts. Notably, around 35% of patients with FCS received novel therapies. Treatment with volanesorsen and lomitapide led to a 62% reduction in triglyceride, with median levels decreasing from 1319 mg/dL to 708 mg/dL. This is consistent with the reductions reported in the clinical trials.[23–27] The lack of a complete data set prevented to assess the safety profile of these drugs. Nevertheless,

we noticed that patients receiving either volanesorsen or lomitapide showed a slightly higher prevalence of hepatic steatosis and modestly increased transaminase levels compared with untreated patients. However, because all patients were already on therapy at the time of enrollment, it was not possible to determine whether these findings are related to the medications themselves. More data are needed to clarify the safety profile of these drugs in the real-world setting. It must be noted that the newer apo CIII–targeting agents, olezarsen, and plozasiran, do not seem to share this adverse effect,[38,39] further supporting apoCIII inhibition as a promising strategy in the treatment of sHTG.

It must be recognized that the present investigation has several limitations. The retrospective design, the relatively small sample size, and the ethnic homogeneity limit the generalizability of our findings. Furthermore, the variability in treatment timing and the lack of detailed lifestyle data presented challenges in evaluating the effects of therapies. Finally, an assessment of the benefits of therapies is hampered by the lack of longitudinal data on clinical outcome variables. In addition, the lack of polygenic risk score analysis limits the assessment of the genetic contribution to MCS, particularly in the vnMCS subgroup. It is imperative that future research incorporates comprehensive baseline phenotypes and a longer follow-up period in larger cohorts of sHTG patients.

CONCLUSIONS

This study provides a detailed characterization of patients with FCS and MCS from the Italian LIPIGEN-sHTG registry, highlighting differences in genetic architecture across populations and underscoring the relevance of ethnicity in interpreting genetic findings. Therapeutically, fibrates and fish oil proved effective in MCS but showed limited impact in FCS. In contrast, novel therapies, such as volanesorsen and lomitapide, demonstrated significant efficacy in FCS, addressing a critical therapeutic gap. However, variability in treatment approaches and the absence of longitudinal data limit definitive conclusions on long-term outcomes. Future research should aim to overcome the current study's limitations through prospective designs, larger sample sizes, and standardized long-term follow-up to further refine diagnostic and therapeutic strategies for sHTG.

ARTICLE INFORMATION

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Supplemental Material

Table S1
Figure S1–S1
Major Resources Tables
STROBE Statement

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