CLINICAL RESEARCH

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HYPERTRIGLYCERIDEMIA IS ASSOCIATED WITH LONG-TERM RISK OF CARDIOVASCULAR EVENTS AND SPECIFIC COMORBIDITY IN VERY HIGH-RISK HYPERTENSIVE PATIENTS

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Although hypertriglyceridemia (HTG) frequently occurs in hypertensive patients and may increase cardiovascular risk, the need for and manner of its reduction remain controversial. The objectives of this study were to compare lipid profiles, parameters of glucose homeostasis, comorbidity, and 5-year survival without cardiovascular events in very high-risk hypertensive (VHRH) patients with and without HTG, who received moderate intensity atorvastatin therapy. After initial assessment, 107 VHRH subjects were divided into two groups, i.e., without (n = 49) and with HTG (n = 58). During observation once annually patients were interviewed about prior hospitalizations with further screening for diabetes. Combined endpoint included hospitalization due acute myocardial infarction, decompensated heart failure, stroke or death. Survival was analyzed by Kaplan-Meier's method. Nonparametric methods were used for statistical analysis. Higher median values of logarithmic value of triglycerides-to-HDL-cholesterol ratio, lipid accumulation product, fasting insulin, and HOMA index were observed in group 2 (P<0.002) that reflect predominance of small dense LDL particles, ectopic lipid deposition and insulin resistance. Patients with HTG more commonly had type 2 diabetes (58.6% vs 34.5%, including first-detected cases during initial assessments and observation, P = 0.02), liver steatosis (81.0% vs 55.1%, P = 0.006), and lithogenic gallbladder disorders (55.2% vs 34.7%, P = 0.05). Women with HTG frequently had a history of hysterovariectomy (55.2% vs 19.0%, P = 0.018). Despite long-term statin therapy, they often failed to reach recommended LDL-C targets and had worse survival due to significantly higher incidence of combined endpoint (39.6% vs 22.4%, P = 0.027). Further studies are necessary to find safe and effective strategy for secondary prevention in this population.

K e y w o r d s: hypertriglyceridemia, very high-risk hypertensive patients, type 2 diabetes, cardiovascular events, atorvastatin therapy.

Introduction

Arterial hypertension is a highly prevalent and well- established modifiable cardiovascular risk factor that is usually associated with many other factors such as dyslipidemia, obesity and diabetes mellitus. Although increased levels of low density lipoprotein cholesterol (LDL-C) is now considered to be the main target for cardiovascular risk reduction [1], there are other atherogenic dyslipidemias, such as decreased serum high density lipoprotein cholesterol (HDL-C) level and hypertriglyceridemia (HTG). Together with hypertension, abdominal obesity and abnormal glucose regulation, these lipid abnormalities form a phenotype of metabolic syndrome that at least doubles the cardiovascular risk [2]. Among hypertensive patients with very high risk all these risk factors often coexist in different combinations and are frequently accompanied by a specific comorbidity that has direct or indirect relation to insulin resistance and obesity (e.g., type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease, polycystic ovary disease, stroke and other neurological disorders, cancer) [2, 3]. In addition, advanced hypertension-mediated organ damage (HMOD) and established atherosclerotic cardiovascular diseases (ASCVD) significantly amplify the risk of future cardiovascular events (CVE) and death in this population [4].

HTG is defined as serum triglyceride (TG) level ≥ 1.7 mmol/l, with further grading into mild, moderate and severe with the cutoff points of 2.3 and 11.2 mmol/l, respectively as proposed by the Endocrine Society in 2012. Mild-to-moderate HTG is associated with higher cardiovascular risk, whereas moderate-to-severe HTG significantly increases the risk of acute pancreatitis [5]. However, the role of HTG as an independent risk factor that increases cardiovascular mortality remains controversial due to: 1) inability of chylomicrons to penetrate the arterial wall, 2) frequent coexistence with other atherogenic types of dyslipidemia, and 3) conflicting results of studies that assessed this influence [1, 5].

The ambiguity of the role of HTG as an independent risk factor makes our research relevant. Our objectives were to compare lipid profiles, parameters of glucose homeostasis, comorbidity, 5-year survival rate and occurrence of CVE in very high-risk hypertensive patients with and without HTG, who received moderate intensity atorvastatin therapy.

Materials and Methods

Design and protocol. This observational prospective study lasted five years (recruitment during December 2009, observation from January 2010 to January 2015). The protocol was approved by the Committee of Ethics at Danylo Halytsky Lviv National Medical University (No 2, March 23, 2009). The first phase included recruitment of patients, initial assessment, and formation of groups. The results of tests obtained during the initial assessment were used to compare metabolic characteristics and comorbidity among participants without and with HTG.

The second phase was aimed to assess the rate of complications (i.e., CVE and new-onset diabetes), and to estimate 5-year survival of participants without and with HTG. Once per year during 60 months, after a telephone call, patients visited the medical office for examination and history taking. All cases of hospitalization for this period were recorded and revised in a hospital database; the causes and outcomes of each hospitalization were defined from medical records. In the absence of hospitalization during this period, fasting glucose was measured in capillary blood, using glucometer Super Glucocard II (Japan); otherwise, the results were taken from medical records. Standard oral glucose tolerance test (OGTT) was conducted after detection of fasting glycemia ≥ 5.6 mmol/l in capillary blood (≥ 6.1 mmol/l in plasma). At the end of the study, serum lipids were measured in all patients, and OGTT was performed for those who remained euglycemic during observation.

Documented cases of hospitalization due to acute myocardial infarction (MI), decompensated heart failure (HF), stroke or death comprised a combined endpoint for CVE. New-onset diabetes was diagnosed when a patient's OGTT results met the criteria for diabetes (fasting glucose level ≥ 7.0 mmol/l and/or 2-hour post-load glucose level ≥ 11.0 mmol/l).

Patients. To recruit the maximal number of participants for the shortest period of time, within one month all very high-risk hypertensive patients who were treated in three different departments of therapy and cardiology at the 1st and 8th Lviv City hospitals that are clinical bases of the Department of Internal Medicine No 2 were selected (*n* = 156). These were patients who met current criteria for the very high-risk category [4]: 1) grade 3 hypertension (blood pressure (BP) levels ≥ 180/110 mm Hg) in combination with HMOD or first detected T2DM without organ damage; and 2) patients with ASCVD, regardless of their BP levels.

To avoid independent influence on survival, the following categories were excluded: 1) all patients with previously diagnosed diabetes of both types (*n* = 28) because all of them had poor glycemic control and severe target organ damage; 2) patients with advanced dysfunction of eliminating organs or severe comorbidity, i.e., liver enzymes ≥ 2-fold above the upper limits of normal (*n* = 6), estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2 (*n* = 5), and malignant tumors (*n* = 2). We also removed from consideration three patients with a history of pancreatitis because, despite association with HTG, pancreatitis was not the subject of our research; moreover, pancreatic damage may cause a specific type of diabetes requiring insulin therapy. In addition, five persons declined to participate.

Hence, 107 very high-risk hypertensive patients (57 men and 50 women) were enrolled in the study after signing written informed consent forms in accordance with the principles of the Declaration of Helsinki, European Convention on Human Rights and Biomedicine, and relevant laws of Ukraine. The reasons for hospitalization were the following: acute ST-elevation myocardial infarction (*n* = 21), decompensated heart failure (*n* = 12), severe stable angina unresponsive to drug therapy (*n* = 34), paroxysmal atrial fibrillation (*n* = 6), and poor control of hypertension (*n* = 34) (Table 1).

The initial assessment was performed after the patient was stabilized before hospital discharge. According to detected serum TG levels, participants were divided into two groups. Group 1 included 49 patients with serum TG levels < 1.7 mmol/l, and the other 58 patients with TG levels ≥ 1.7 mmol/l comprised group 2.

In group 1 there were 28 men and 21 women. Group 2 included an equal number of both genders (*n* = 29), among them 35 patients with mild HTG (18 men, 17 women) and 23 with moderate HTG (11 men, 12 women). The women tended to be older than the men, but the gender difference was statistically significant only among patients with moderate HTG. Medians of age in years with [lower; upper quartiles] in men versus women were as follows: 63.5 [54.0; 69.5] vs 67.0 [60.0; 72.0] in group 1 (P = 0.29); 57.0 [47.0; 70.0] vs 62.0 [60.0; 70.0] among patients with mild HTG (*P* = 0.31) and 56.0 [49.0; 58.0] vs 68.0 [62.0; 73.5] in those with moderate HTG (*P* = 0.009).

Participants received standard therapy currently recommended for patients with very high risk hypertension [4]. All patients received aspirin (75-100 mg daily) and atorvastatin (20-40 mg daily) for secondary prevention. To achieve BP goals, all patients received dual antihypertensive therapy with a fixed-dose combination of an ACE inhibitor (enalapril 10-20 mg, ramipril 5 mg or perindopril 4-8 mg) or angiotensin receptor blocker (valsartan 80-160 mg) with thiazide (hydrochlorothiazide 12.5-25 mg) or thiazide-like diuretic (indapamide 1.25-2.5 mg) once a day. A beta-blocker (bisoprolol 5-10 mg, carvedilol 12.5-25 mg or nebivolol 5 mg) or calcium channel blocker (amlodipine 5-10 mg) was used as a third antihypertensive agent, depending on individual specific indications and contraindications. Patients with HF additionally received mineralocorticoid receptor antagonists (spironolactone 25 mg or eplerenone 25 mg once a day). Patients with first detected T2DM during initial assessment (*n* = 24) were consulted by endocrinologists and metformin therapy (500 mg → 850 mg once a day) was initiated. Classes of medications and percentages of users are summarized in Table 1.

Tests and methods used for the initial assessment. All participants underwent anthropometry with measurements of height, body weight, body mass index (BMI = height in m/[body weight in kg]^2), waist and hip circumferences and their ratio (WHR); abdominal ultrasonography, and transthoracic Doppler echocardiography. Liver steatosis was diagnosed in the presence of the following ultrasonographic signs: diffusely hyperechoic liver, poor visualization of the walls of the portal veins, or dorsal attenuation of echo-signal. Ultrasonographic gallbladder assessment included size and wall thickness measurements and detection of biliary sludge, gallstones or the state after cholecystectomy. The criterion of left ventricular (LV) hypertrophy was echocardiographic LV mass index >50 g/m$^{2.7}$ for men and >47 g/m$^{2.7}$ for women [4].

Laboratory tests included renal and liver function tests (standard kits CORMAY, Poland). Glomerular filtration rate was estimated by the Modification of Diet in Renal Disease (MDRD) equation. Serum high sensitive C-reactive protein levels were detected by enzyme-linked immunosorbent assay, using a standard kit HEMA (Russia), and fibrinogen level was measured by gravimetric method.

Serum levels of total cholesterol (TC), TG, and HDL-C were measured by enzymatic methods, using standard kits HUMAN (Germany). The LDL-C was calculated using Friedewald's equation. The logarithmic value of TG-to-HDL-C ratio was calculated as an indicator of LDL particle size, i.e., a zero value of Log (TG/HDL-C) corresponds to a LDL particle diameter of 25.5 nm that delimits normal type A (negative values) from atherogenic type B (positive values) [6]. Lipid accumulation product (LAP) was calculated as follows: LAP = (WC – 58)×TG for women, LAP = (WC – 65)× G for men, where WC – waist circumference in cm, TG – serum triglyceride level in mmol/l [7].

Glycated hemoglobin (HbA1c) was measured in venous blood by ion exchange chromatography with a standard kit HUMAN (Germany). Standard OGTT was performed with blood sampling 10 h after overnight fast and at 30, 60, and 120 min after oral administration of 75 g of glucose dissolved in water. Plasma glucose levels were measured by glucose oxidase method, and serum insulin and C-peptide levels were assessed by solid phase enzyme immunosorbent assay on "TECAN sunrise remote/touch screen F 039300" analyser using standard kits DRG Instrumentals GmbH (Germany). The following insulin sensitivity indices were calculated [8]:

$$\text{HOMA index} = I_{0'} \times G_{0'}/22.5,$$

where HOMA – homeostasis model assessment, $I_{0'}$ – fasting insulin level in μU/ml, $G_{0'}$ – fasting glucose level in mmol/l;

$$\text{DeFronzo index} = \text{incAUC I/G}_{0'-120'} \times [10000/\sqrt{(I_{0'} \times G_{0'}) \times (I_m \times G_m)}],$$

where incAUC $I/G_{0'-120'}$ – ratio of incremental area under the insulin curve to incremental area under the glucose curve during OGTT that were calculated according to the trapezoid rule. The formula in square brackets represents the Matsuda index, where $I_{0'}$ – fasting insulin level, I_m – mean insulin level during OGTT in μU/ml; $G_{0'}$ – fasting glucose level, G_m – mean glucose level during OGTT in mg/dl.

Statistical analysis was performed using the program Statistica for Windows 6.0 (Statsoft, USA). Since Shapiro-Wilk's test did not show normal distribution of the majority of analyzed parameters, non-parametric methods were used. Relative values were presented in percentages; the χ^2-test or Fisher's exact test were used for group comparison. Quantitative values were presented as median [lower; upper quartiles], and groups were compared by the Mann-Whitney U-criterion. Associations between variables were estimated using Kendall rank correlation coefficient (τ). Survival was analyzed by the Kaplan-Meier method, estimating the cumulative proportion surviving, and the difference between groups was defined by the Cox (F)-test. *P* values less than 0.05 were considered statistically significant. To reduce the chance of type I error, Bonferroni correction was applied when multiple variables were compared.

Results

Data obtained during the initial assessment are summarized in Table 1.

There were not statistically significant differences between groups by age, number of (ex-) smokers and persons with excessive alcohol intake. Since all patients had excessive body weight and hypertension, median values of anthropometric parameters and BP did not differ significantly, as well as heart rate and median levels of fibrinogen and C-reactive protein.

Regarding HMOD, approximately two-thirds of participants had left ventricular hypertrophy, more than half had proteinuria and moderate chronic kidney disease, more than one third had signs of arterial stiffening and atherosclerosis of peripheral arteries indicated by high pulse pressure and decreased ankle-brachial index, and one fifth had hypertensive retinopathy with exudates or haemorrhages. Differences between groups were not statistically significant for any of these abnormalities.

In view of the fact that all participants had very high-risk hypertension, the number of patients with acute or prior MI, stable angina, prior stroke or transient ischemic attack, peripheral artery disease, HF with preserved or reduced ejection fraction, atrial fibrillation and first detected T2DM did not reach statistically significant differences between groups.

The majority of participants had elevated levels of TC and LDL-C in combination with low HDL-C level (42.9% in group 1 and 41.4% in group 2) or normal HDL-C level (24.5% and 25.9%, respectively). As the TG level was the grouping parameter, its median value in group 2 was significantly and almost two times higher than in group 1. There were no significant differences in median values of HbA1c, TC, HDL-C, and LDL-C. In contrast, median values of Log (TG/HDL-C), LAP, glycemia in all points of OGTT, fasting insulin, C-peptide, and HOMA index were significantly higher, whereas median values of Matsuda and DeFronzo indices were significantly lower in group 2 compared with group 1 (Table 2).

Hence, among lipid parameters only Log (TG/HDL-C) and LAP differed significantly, being higher in patients with HTG. The first parameter indicates the prevalence of small dense LDL particles, a qualitative lipid abnormality that commonly occurs in diabetic dyslipidemia. Higher LAP values suggest that HTG is associated with abdominal obesity and ectopic lipid deposition beyond adipose tissue (visceral obesity), e.g., in the liver, pancreatic β-cells, or skeletal muscles. Such ectopic deposits may decrease β-cell function, cause insulin resistance, lipotoxicity, and promote non-alcoholic fatty liver disease [9]. This may explain the high prevalence of liver steatosis in patients with HTG (81.0% vs 55.1% in group 1, P = 0.006). Another contributive factor for

Table 1. Baseline characteristics of participants with normotriglyceridemia (group 1) and hypertriglyceridemia (group 2)

Parameter, units	Group 1 (*n* = 49)	Group 2 (*n* = 58)	*P* value
Causes of initial hospitalization			
Acute ST-elevation myocardial infarction, %	14.2	24.2	0.230
Decompensation of heart failure, %	14.3	8.6	0.376
Severe stable angina unresponsive to therapy %	32.7	31.0	1.00
Paroxysmal atrial fibrillation, %	12.2	10.3	0.769
Poor control of hypertension	28.6	34.5	0.539
Risk factors			
Age, years	66.0 [58.0; 71.0]	61.5 [53.0; 70.0]	0.237
Smoking (current or prior), %	36.7	27.6	0.401
Excessive alcohol use, %	10.2	6.9	0.729
Body mass index, kg/m^2	30.0 [27.0; 34.4]	30.7 [28.1; 33.3]	0.523
Obesity (body mass index ≥ 30 kg/m^2), %	51.0	62.1	0.327
Waist circumference in men, cm	110 [102; 117]	109 [105; 113]	0.868
Waist circumference in women, cm	98 [89; 117]	99 [93; 113]	0.922
Hip circumference in men, cm	109 [103; 117]	110 [106; 114]	0.843
Hip circumference in women, cm	108 [102; 123]	108 [102; 122]	0.876
Waist-to-hip ratio in men	0.99 [0.96; 1.03]	1.00 [0.96; 1.02]	0.814
Waist-to-hip ratio in women	0.90 [0.87; 0.95]	0.91 [0.86; 0.94]	0.755
Systolic blood pressure, mm Hg	140 [130; 160]	140 [125; 155]	0.453
Diastolic blood pressure, mm Hg	85 [80; 100]	85 [80; 90]	0.753
Hypertensive crises, %	53.1	62.1	0.432
Heart rate, beats per minute	79 [70; 94]	78 [67; 91]	0.503
Fibrinogen, g/l	3.4 [2.8; 4.1]	3.7 [3.0; 4.0]	0.539
C-reactive protein, mg/l	13.5 [10.3; 15.3]	13.4 [11.5; 16.0]	0.629
Type 2 diabetes detected during the initial assessment, %	14.3	29.3	0.102
Hypertension-mediated organ damage			
Left ventricular hypertrophy, %	69.3	79.3	0.170
Proteinuria, %	57.1	60.3	0.844
Estimated glomerular filtration rate, ml/min/1.73m^2	54.8 [45.7; 76.2]	58.0 [41.4; 74.0]	0.720
Moderate chronic kidney disease[1], %	59.2	51.7	0.559
Pulse pressure ≥60 mmHg, %	49.0	32.8	0.114
Ankle-brachial index <0.9, %	40.8	30.5	0.317
Retinopathy with exudates and hemorrhages	20.4	20.5	1.00
Established cardiovascular diseases			
Acute ST-elevation myocardial infarction, %	14.2	24.2	0.230
Stable angina III-IV classes[2] %	57.1	60.3	0.844
Prior myocardial infarction, %	44.9	37.9	0.555
Prior stroke or transient ischemic attack, %	32.7	41.4	0.424

Table 1. (Continuation)

Parameter, units	Group 1 (*n* = 49)	Group 2 (*n* = 58)	*P* value
Peripheral artery disease, %	32.7	27.6	0.673
- typical (exertional intermittent claudication), %	4.1	-	0.215
- asymptomatic (documented by ADU[3]), %	28.6	27.6	1.00
Heart failure with reduced ejection fraction, %	14.3	8.6	0.376
Heart failure with preserved ejection fraction, %	46.9	62.1	0.125
Atrial fibrillation, %	24.5	10.3	0.070
Medications used by participants			
Aspirin, %	100	100	–
Atorvastatin, %	100	100	–
ACE[4] inhibitor or angiotensin receptor blocker, %	100	100	–
Thiazide or thiazide-like diuretic, %	100	100	–
Beta-blocker, %	69.4	63.8	0.682
Calcium channel blocker, %	30.6	32.8	0.838
Mineralocorticoid receptor antagonists, %	14.3	8.6	0.376
Metformin, %	14.3	29.3	0.102

Notes: [1]Estimated glomerular filtration rate within range of 30 to 60 ml/min/1.73 m^2; [2]Canadian Cardiovascular Society Functional Classification of stable angina pectoris; [3]ADU – arterial duplex ultrasonography; [4]ACE – angiotensin-converting enzyme.

liver steatosis is hyperinsulinemia that was also typical for patients with HTG with a significant difference at the fasting point (Table 2). A strong direct correlation was observed between liver steatosis and severity of HTG (τ = 0.242, P = 0.0002). As we had excluded from the study all patients with elevated liver enzymes meeting the criterion for hepatocellular damage, the median values of alanine aminotransferase, aspartate aminotransferase and γ-glutamyltransferase did not significantly differ between groups, and there were no cases of steatohepatitis among participants.

Apart from fasting hyperinsulinemia and insulin resistance, HTG was associated with impaired β-cell ability to respond adequately to glucose load, as indicated by the presence of post-load hyperglycemia, significantly lower Matsuda index and twice lower median values of the DeFronzo index. Because post-load hyperglycemia is a surrogate marker of the postprandial state, we may conclude that patients with HTG tended to have extended hyperglycemic episodes after meals. Despite all these abnormalities, the difference in HbA1c was not statistically significant between groups. Such discrepancies between glycemia and HbA1c are described in the literature [10]. Inadequate postprandial insulin response and impaired insulin sensitivity may explain the high incidence of new-onset T2DM in our participants. During the period of observation, 27 new cases of diabetes were diagnosed (23.8% in group 1 and 41.5% in group 2). The cumulative proportions who survived after 60 months were 75.8% in group 1 and 58.5% in group 2 (P = 0.035) (Fig. 1).

Among 17 converters with HTG, ten had mild and seven had moderate elevation of serum TG levels. Transformation to T2DM positively correlated with the severity of HTG (τ = 0.288, P = 0.023). Among converters, 81.5% had elevated baseline LDL-C, and 55.5% had decreased baseline HDL-C levels. Diabetes did not develop among group 1 patients who reached target LDL-C <1.8 mmol/l under statin therapy, whereas in group 2 it was detected in five patients who had achieved the target (P_{1-2} = 0.026).

Patients with first detected T2DM during initial assessment (n = 24) and those who converted to diabetes during observation were managed by endocrinologists and all had good glycemic control at the end of the study (HbA1c ≤ 6.5%), receiving metformin monotherapy. Taking together the patients with initially detected T2DM and converters, the difference between groups was significant (n = 17

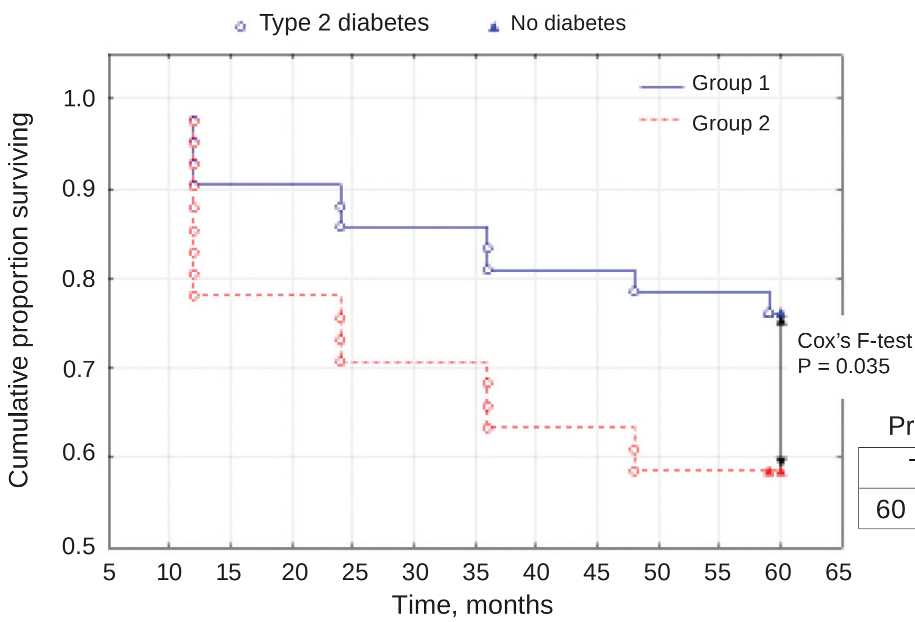
Table 2. Baseline lipids and parameters of glucose regulation in participants with normotriglyceridemia (group 1) and hypertriglyceridemia (group 2)

Parameter, units	Group 1 (n = 49)	Group 2 (n = 58)	P value
Triglycerides, mmol/l	1.28 [0.9; 1.45]	2.15 [1.8; 2.70]	<0.0001*
Total cholesterol, mmol/l	5.4 [4.5; 6.1]	5.6 [4.8; 6.3]	0.225
HDL cholesterol, mmol/l	1.00 [0.90; 1.37]	0.96 [0.88; 1.40]	0.697
LDL cholesterol, mmol/l	3.5 [2.5; 4.4]	3.4 [2.3; 4.1]	0.371
Log(TG/HDL-C)	-0.11 [-0.11; 0.16]	0.32 [0.21; 0.42]	<0.0001*
Lipid accumulation product, cm×mmol/l	48.4 [40.3; 70.4]	97.3 [79.5; 112.5]	<0.0001*
Glycated hemoglobin, %	5.1 [4.5; 5.8]	5.4 [4.5; 6.2]	0.175
$Glucose_{0'}$, mmol/l	6.1 [4.8; 6.4]	6.4 [6.0; 6.9]	0.0059
$Glucose_{30'}$, mmol/l	8.8 [6.8; 9.9]	9.7 [8.0; 10.8]	0.0254
$Glucose_{60'}$, mmol/l	9.6 [7.8; 11.5]	11.0 [9.8; 13.0]	0.0067
$Glucose_{120'}$, mmol/l	8.0 [6.4; 10.8]	9.7 [6.8; 12.3]	0.0303
$Insulin_{0'}$ μU/ml	12.8 [9.1; 18.7]	16.3 [13.7; 24.8]	0.0015*
$Insulin_{30'}$, μU/ml	40.8 [27.5; 69.5]	49.9 [32.5; 70.3]	0.240
$Insulin_{60'}$, μU/ml	67.6 [38.3; 90.3]	77.1 [41.6; 95.5]	0.189
$Insulin_{120'}$, μU/ml	54.8 [32.5; 72.7]	65.7 [41.9; 85.0]	0.115
$C\text{-}peptide_{0'}$, ng/ml	1.99 [1.00; 3.89]	3.30 [2.15; 5.70]	0.0026
$C\text{-}peptide_{120'}$, ng/ml	6.50 [2.88; 12.10]	8.10 [4.65; 12.90]	0.191
HOMA index	3.67 [2.38; 5.50]	5.78 [3.41; 7.54]	0.0015*
Matsuda index	4.03 [2.80; 6.54]	3.04 [2.20; 3.96]	0.0027
DeFronzo index	62.5 [37.0; 112.3]	31.0 [18.0; 70.2]	0.0047

Note: *Statistically significant after Bonferroni correction (P < 0.0025).

(34.7%) in group 1 and n = 34 (58.6%) in group 2, P = 0.02).

Another common comorbidity was lithogenic gallbladder disorders that were detected by ultrasonographic evidence of biliary sludge, presence of gallstones or prior cholecystectomy due to gallstone disease or calculous cholecystitis. Such abnormalities were found in 55.2% of patients with HTG compared to 34.7% in group 1 (P = 0.05), and directly correlated with severity of HTG (τ = 0.133, P = 0.041). Both overweight and insulin resistance are well-established risk factors for gallstone disease, but it is unclear whether HTG causes cholelithiasis or is merely associated with the disease. Bile composition (e.g., cholesterol supersaturation), impaired motility of the gallbladder, inflammation and hypersecretion of mucin gel in the gallbladder, slower motility of the colon and enhanced intestinal cholesterol absorption promote the formation of cholesterol stones. Cholesterol supersaturation of bile is associated more with obesity than with HTG [11]. However, HTG may cause gallbladder hypokinesia because it inhibits sensitivity to cholecystokinin that regulates postprandial contraction of the gallbladder [12] that may promote cholesterol crystallization. This explains the higher prevalence of biliary sludge and cholelithiasis in patients with HTG. Under the influence of lipid-lowering therapy, e.g., fibrates or fish oil, the sensitivity of the gallbladder to cholecystokinin may be restored [11, 12]. However, fibrates that are recommended for patients with HTG who are at the LDL-C goal [1] may increase the risk of cholelithiasis, increasing bile cholesterol saturation and decreasing bile acid synthesis [12]. The results of recent meta-analysis demonstrated that statin therapy might decrease the risk of gallstone disease [13], but underlying mechanisms of this beneficial effect need to be elucidated. Statins also showed beneficial effects in the case of non-alcoholic fatty liver disease [14].



Proportion surviving by group

Time	Group 1	Group 2
60 months	75.8%	58.5%

Fig. 1. Kaplan-Meier survival curves when new-onset diabetes was considered as an endpoint

In addition, more than half of female participants with HTG had prior hysterovariectomy (55.2% compared with 19.0% in group 1, $P = 0.018$). Similar results were observed in a large retrospective cohort study, where the prevalence of hyperlipidemia was 1.3 times higher after hysterectomy, and 1.9 times higher after hysterovariectomy compared to the control group [15].

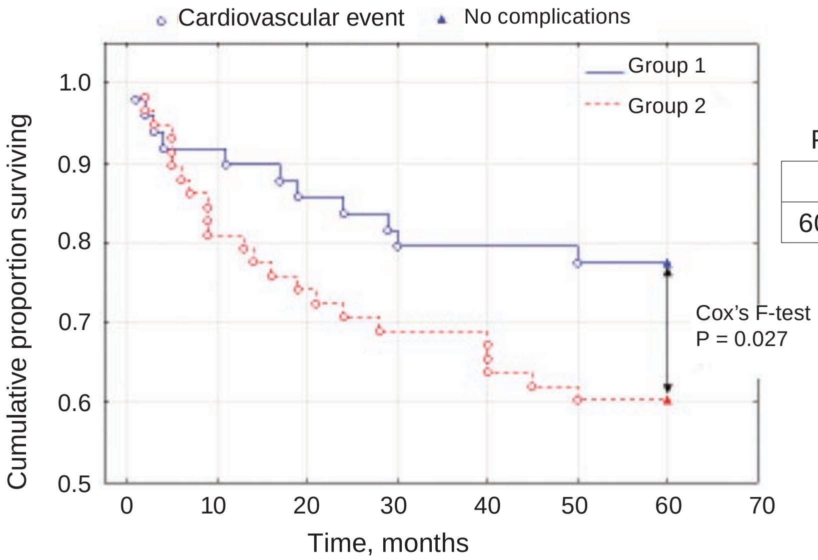
However, the most important study finding was a significantly higher occurrence of CVE among patients with HTG. During 60 months, 11 patients (22.4%) in group 1 and 23 patients (39.6%) in group 2 had reached the combined endpoint (Fig. 2). The cumulative proportion surviving at the end of observation were 77.5% in group 1 and 60.3% in group 2 ($P = 0.027$).

The grade of HTG directly and significantly correlated with CVE ($\tau = 0.177$, $P = 0.007$). Despite the long-term atorvastatin therapy, at the end of observation 79.4% of patients with CVE did not reach even the previously recommended LDL-C target of < 1.8 mmol/l. Moreover, in group 1 only one CVE was documented among patients who had reached this level, compared with 6 cases in group 2 ($P = 0.38$). In 2019 the LDL-C target for patients with very high risk was been decreased to < 1.4 mmol/l [1]. In this case, practically all participants (99.1%) did not reach the recommended goal at the end of observation.

Discussion

These findings suggest that very high-risk hypertensive patients require a more aggressive statin regimen or its combination with the cholesterol absorption inhibitor ezetimibe and/or proprotein convertase subtilisin/kexin type 9 (PCSK 9) inhibitors, as recommended by the 2019 ECS/EAS guidelines [1]. However, taking into account metabolic disorders and high risk of diabetes in participants with HTG, the intensification of statin therapy will further increase the risk, as the diabetogenic effect of this drug class is dose-dependent [16]. Thus, to avoid dose escalation, the combination of statin with either ezetimibe or PCSK 9 inhibitor or monotherapy with these agents seems to be a better approach for persons with HTG. Both classes demonstrated ASCVD risk reduction in direct correlation with the achieved lowering of LDL-C, even in the diabetic population, and have not been reported to increase the risk of diabetes [1]. However, longer post-marketing experience may also add some adverse effects to their safety profiles.

Nonetheless, any of these agents is not a primarily TG-lowering medication. Besides, the analysis of long-term clinical outcomes in participants of two randomized controlled studies (dal-OUTCOMES and MIRACL) suggest that HTG increases the risk of the second ischemic coronary event even in those who have reached target LDL-C under lipid-lowering therapy [17].



Proportion surviving by group

Time	Group 1	Group 2
60 months	77.5	60.3

Clinical outcomes after 5 years of observations	Group 1		Group 1	
	N	%	N	%
No documented events	38	77.6	35	60.4
Acute myocardial infarction	6	12.2	9	15.5
Decompensated heart failure	1	2.05	5	8.6
Stroke	1	2.05	5	8.6
Death	3	6.1	4	6.9

Fig. 2. Kaplan-Meier survival curves when cardiovascular events were considered as a combined endpoint and the number of events occurred in groups

Among specific TG-lowering agents, fibrates and omega-3 polyunsaturated fatty acids may be considered. As was mentioned above fibrates are formally contraindicated in preexisting gallbladder diseases, and their efficacy to reduce the cardiovascular risk remains controversial [5]. A recent meta-analysis incorporating data from 13 randomized controlled trials suggested that marine omega-3 supplementation at higher doses had been associated with lower risk of ASCVD, MI and cardiovascular death, even after exclusion of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT). The REDUCE-IT included high-risk patients with HTG on effective statin therapy and demonstrated a 25% risk reduction in subjects who received a high dose of icosapent ethyl (a highly purified form of eicosapentaenoic acid) compared with placebo. Moreover, the reduction in CVE was greater than the reduction in TG levels and did not correlate with either baseline or on-trial TG values [18]. Considering these promising results and specific comorbidity associated with HTG, marine omega-3 supplementation might be useful for this population.

Conclusions

Compared with very high risk hypertensive patients without HTG, in the group with HTG significantly higher median values of Log (TG/HDL-C), LAP, fasting insulin, and HOMA index were observed that reflect predominance of small dense LDL particles, ectopic lipid deposition and insulin resistance. Patients with HTG had a higher risk of T2DM (58.6% vs 34.5%, including first-detected cases during initial assessments and observation, $P = 0.02$), liver steatosis (81.0% vs 55.1%, $P = 0.006$), and lithogenic gallbladder disorders (55.2% vs 34.7%, $P = 0.05$). Women with HTG frequently had a history of hysterovariectomy (55.2% vs. 19.0%, $P = 0.018$). Despite long-term moderate intensity atorvastatin therapy, patients with HTG often failed to reach recommended LDL-C targets and had worse survival due to significantly higher incidence of composite endpoint including hospitalization due to acute myocardial infarction, decompensated heart failure, stroke or death (39.6% vs. 22.4%, $P = 0.027$).

Further studies are needed to elucidate a way of lipid-lowering therapy in this population. Intensification of statin therapy may further increase the risk of diabetes. Fibrates pose the risk of cholelithiasis and should be avoided in many of such patients. Promising perspectives are ezetimibe, PCSK 9 inhibitors and murine omega-3 polyunsaturated fatty acids.

Conflict of interest. Authors have completed the Unified Conflicts of Interest form at http://ukrbiochemjournal.org/wp-content/uploads/2018/12/coi_disclosure.pdf and declare no conflict of interest.

Ethical Committee or Institutional Animal Care and Use Committee Approval: approved by the Ethics Committee at Danylo Halytsky Lviv National Medical University, protocol number 3, dated by March 23, 2009.

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ГІПЕРТРИГЛІЦЕРИДЕМІЯ АСОЦІЮЄТЬСЯ З ДОВГОСТРОКОВИМ РИЗИКОМ СЕРЦЕВО-СУДИННИХ УСКЛАДНЕНЬ ТА СПЕЦИФІЧНОЮ КОМОРБІДНІСТЮ У ХВОРИХ НА АРТЕРІАЛЬНУ ГІПЕРТЕНЗІЮ З ДУЖЕ ВИСОКИМ РИЗИКОМ

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Хоча гіпертригліцеридемія (ГТЕ) часто виявляється у хворих на артеріальну гіпертензію та може підвищувати ризик серцево-судинних ускладнень, необхідність її зниження та шляхи доволі дискусійні. Метою цього дослідження було порівняння показників ліпідів крові, параметрів гомеостазу глюкози, коморбідності та 5-річного виживання без серцево-судинних ускладнень у пацієнтів з дуже високим ризиком гіпертензії з/без ГТЕ, котрі отримували терапію аторвастатином помірної інтенсивності. Після початкового обстеження, 107 таких пацієнтів було поділено на дві групи – без ГТЕ (*n* = 49, група 1) та з ГТЕ (*n* = 58, група 2). Впродовж 5 років проводилось щорічне опитування пацієнтів щодо попередніх госпіталізацій та скринінг діабету. Причини, перебіг та наслідки госпіталізацій з'ясовувались на підставі медичної документації. Госпіталізація з приводу гострого інфаркту міокарда, інсульту, декомпенсації серцевої недостатності або смерть були включені у комбіновану кінцеву точку серцево-судинних проявів. Виживання аналізували методом Каплана-Мейера. Для статистичної обробки результатів використовували непараметричні методи. У групі 2 виявлено вищі медіани логарифмічного відношення тригліцеридів до холестеролу ліпопротеїнів високої щільності, продукту акумуляції ліпідів, рівня інсуліну натще та індексу HOMA ($P < 0.002$), що вказувало на переважання малих щільних часточок ліпопротеїдів низької щільності, ектопічне відкладання жиру та резистентність до інсуліну. У пацієнтів з ГТЕ частіше виявляли цукровий діабет 2 типу (58,6% у порівнянні з 34,5% у групі 1, включаючи вперше виявлені випадки під час початкового обстеження та нові випадки впродовж 5-річного спостереження $P = 0{,}02$), стеатоз печінки (81,0% у порівнянні з 55,1%, $P = 0{,}006$) та літогенні розлади жовчного міхура (55,2% у порівнянні з 34,7%, $P = 0{,}05$). У жінок з ГТЕ частіше спостерігали гістероваріектомію в анамнезі (55,2% проти 19,0% у групі 1, $P = 0{,}018$). Не зважаючи на тривалу терапію аторвастатином у дозі 20–40 мг, пацієнти часто не досягали рекомендованих рівнів ліпопротеїнів низької щільності та мали гірші показники виживання через більшу кількість серцево-судинних ускладнень (39,6% у порівнянні з 22,4% у групі 1, $P = 0{,}027$). Зважаючи на те, що інтенсифікація статинотерапії посилить ризик спричинення діабету, пошук ефективної та безпечної стратегії вторинної профілактики у цій когорті пацієнтів є необхідним і вимагає подальших досліджень.

К л ю ч о в і с л о в а: гіпертригліцеридемія, пацієнти з дуже високим ризиком гіпертензії, діабет 2 типу, терапія аторвастатином.

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