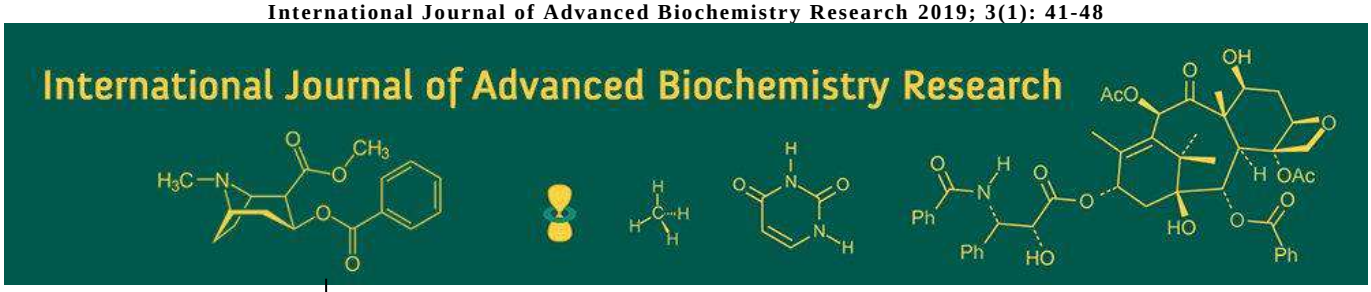


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# Hypertriglyceridemia is associated with long-term risk of cardiovascular events and specific co-morbidity in very high risk hypertensive patients

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**Abstract**
Although hypertriglyceridemia (HTG) frequently occurs in hypertensive patients and may increase cardiovascular risk, the need and way of its reduction remain controversial. The objectives of the research was to compare lipid profiles, parameters of glucose homeostasis, comorbidity, a 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 interviewing 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 composite endpoint (39.6% vs 22.4%, P=0.027). Further researches are necessary to find safe and effective strategy for secondary prevention in this population.

**Keywords:** Hypertriglyceridemia, hypertension, diabetes, cardiovascular events, very high risk, secondary prevention, atorvastatin

## Introduction
Arterial hypertension is highly prevalent and well- established modifiable cardiovascular risk factor that usually is 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 cardiovascular risk [2]. Among hypertensive patients with very high risk all these risk factors often coexist in different combinations and frequently accompanied by 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 and death in this population [4].
Hypertriglyceridemia 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 mmol/l 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 risk of acute pancreatitis [5]. However, its role as an independent risk factor that increases cardiovascular mortality remains controversial due to 1) inability of chylomicrons to penetrate arterial wall, 2) frequent coexisting with other atherogenic types of dyslipidemia, and 3) conflicting results of studies that assessed this influence [1, 5].

This ambiguity makes the relevance of our research, objectives of which was to compare lipid profiles, parameters of glucose homeostasis, comorbidity, a 5-year survival and occurrence of cardiovascular events (CVE) in very high risk hypertensive patients with and without HTG, who received moderate intensity atorvastatin therapy.

## Materials and methods

Design and protocol. This is observational prospective research lasted five years. The protocol was approved by the Committee of Ethics in 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 annually during 60 months, after a telephone call, patients visited 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 glycaemia ≥ 5.6 mmol/l in capillary blood (≥ 6.1 mmol/l in plasma). In the end of the research, 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. A new-onset diabetes was diagnosed when patient's OGTT results met 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 maximal amount of participants for the shortest period of time, within one month all very high risk hypertensive patients that were treated in three different departments of therapy and cardiology in the 1st and the 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 criteria for very high risk category according to 2018 ESC/ESH guidelines [4]: 1) grade 3 hypertension (blood pressure (BP) levels ≥ 180/110 mm Hg) in combination with HMOD or first detected type 2 diabetes mellitus (T2DM) without organ damage; 2) patients with ASCVD, regardless 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 everybody 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 specific type of diabetes requiring insulin therapy. Five persons refused to participate. Hence, 107 very high-risk hypertensive patients (57 men and 50 women) enrolled the research after signing written informed consents in accordance with the principles of the Declaration of Helsinki, European Convention on Human Rights and Biomedicine, and relevant laws of Ukraine.

The initial assessment was performed after patient's stabilization 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, other 58 patients with TG levels ≥ 1.7 mmol/l comprised group 2.

Thus, in group 1 there were 28 men and 21 women. Group 2 included 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). Females tended to be older than males, but gender difference was statistically significant only among patients with moderate HTG. Medians of age in years with [lower; upper quartiles] in males versus females 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 recommended for patients with very high risk [4]. All patients received aspirin (75-100 mg daily) and atorvastatin (20-40 mg daily) for secondary prevention. To achieve blood pressure goals, 100% of patients received dual antihypertensive therapy with a fixed-dose combination of 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 percent 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, dorsal attenuation of echo-signal.

Ultrasonographic gallbladder assessment included size and wall thickness measurements and detection of biliary sludge, gallstones or a 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 according to 2018 ECS/ESH guidelines [4].

Laboratory tests included renal and liver function tests (standard kits CORMAY, Poland). Glomerular filtration rate was estimated by 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 the 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 females, LAP = (WC - 65) × TG for males, where WC – waist circumference in cm, TG – serum triglyceride level in mmol/l [7].

Glycated haemoglobin (HbA1c) was measured in the venous blood by ion exchange chromatography with a standard kit HUMAN (Germany). Standard OGTT was performed with blood sampling 10 hours after overnight fast and at 30, 60, and 120 minutes after oral administration of 75 g of glucose dissolved in water. Plasma glucose levels were measured by glucose oxidase method, 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]:

- 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
- DeFronzo index = incAUC $I/G_{0'–120'}$ × [10000 / √ ($I_{0'} \times G_{0'}$) × ($I_m \times G_m$)], where incAUC $I/G_{0'–120'}$ – incremental area under the insulin curve to incremental area under the glucose curve ratio during OGTT that were calculated according to trapezoid rule. The formula in square brackets represents 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 $\chi^2$-test or Fisher's exact test were used for group comparison. Quantitative values were presented as median [lower; upper quartiles], groups were compared by Mann-Whitney U-criterion. Associations between variables were estimated using Kendall rank correlation coefficient (τ). Survival was analyzed by Kaplan-Meier method, estimating the cumulative proportion surviving, 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 had been applied when multiple variables were compared.

## Results and Discussion

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

**Table 1:** Baseline characteristics of participants

| Parameter, units | Group 1 (n=49) | Group 2 (n=58) | P value |
|---|---|---|---|
| **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 males, cm | 110 [102; 117] | 109 [105; 113] | 0.868 |
| Waist circumference in females, cm | 98 [89; 117] | 99 [93; 113] | 0.922 |
| Hip circumference in males, cm | 109 [103; 117] | 110 [106; 114] | 0.843 |
| Hip circumference in females, cm | 108 [102; 123] | 108 [102; 122] | 0.876 |
| Waist-to-hip ratio in males | 0.99 [0.96; 1.03] | 1.00 [0.96; 1.02] | 0.814 |
| Waist-to-hip ratio in females | 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 |
| Left ventricular hypertrophy, % | 69.3 | 79.3 | 0.170 |
| 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 haemorrhages | 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 |
| 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 |

Footnotes: [1]Estimated glomerular filtration rate within ranges from 30 to 60 ml/min/1.73m$^2$; [2] Canadian Cardiovascular Society Functional Classification of Stable Angina Pectoris; [3] ADU – arterial duplex ultrasonography; [4] ACE – angiotensin-converting enzyme.

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 blood pressure did not differ significantly, as well as heart rate and median levels of fibrinogen and C-reactive protein.

Speaking about 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 all participants had very high risk, 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 values between groups.

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 TG level was the grouping parameter, its median value in group 2 was significantly and almost twice higher comparing with 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, glycaemia 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 comparing with group 1 (Table 2).

**Table 2:** Baseline lipids and parameters of glucose regulation

| 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-$peptide_{0'}$, ng/ml | 1.99 [1.00; 3.89] | 3.30 [2.15; 5.70] | 0.0026 |
| C-$peptide_{120'}$, 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 ($P < 0.0025$)

Hence, among lipid parameters only Log (TG/HDL-C) and LAP differed significantly, being higher in patients with HTG. The first parameter indicates on prevalence of small dense LDL particles, a qualitative lipid abnormality that commonly occurs in diabetic dyslipidemia. Higher LAP values suggests 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, lipotoxisity, and promote non-alcoholic fatty liver disease [9]. This may explain high prevalence of liver steatosis in patients with HTG (81.0% vs 55.1% in group 1, P = 0.006). Another contributive factor for liver steatosis is hyperinsulinemia that also was typical for patients with HTG with significant difference at fasting point (table 2). Strong direct correlation was observed between liver steatosis and severity of HTG (τ = 0.242, P = 0.0002). As we excluded all patients with elevated liver enzymes meeting the criterion for hepatocellular damage, median values of alanine aminotransferase, aspartate aminotransferase and γ-glutamyl transferase 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 presence of post load hyperglycemia, significantly lower Matsuda index and twice lower median values of deFronzo index. Because post load hyperglycemia is a surrogate marker of 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 glycaemia and HbA1c are described in the literature [10]. Inadequate postprandial insulin response and impaired insulin sensitivity may explain high incidence of new-onset T2DM in our participants. During the period of observation, 27 new cases of diabetes were detected (23.8% in group 1 and 41.5% in group 2). Cumulative proportion surviving were 75.8% and 58.5%, respectively (P = 0.035), see Figure 1.

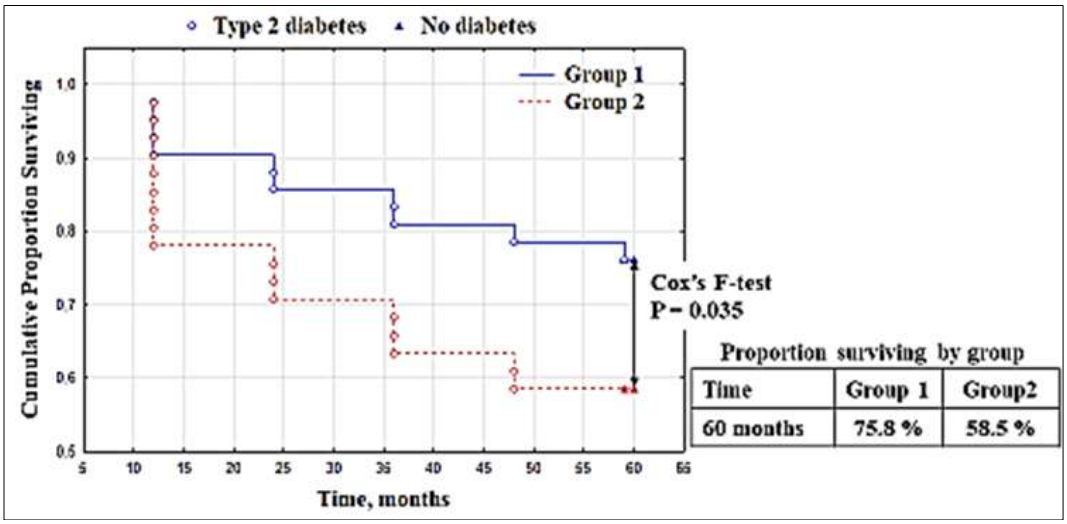



**Fig 1:** Kaplan-Meier survival curves when a new-onset diabetes was taken as an endpoint

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 developed 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 in the end of the research (HbA1c ≤ 6.5%), receiving metformin monotherapy. Taking together patients with initially detected T2DM and converters, the difference between groups was significant (n = 17 (34.7%) in group 1 and n = 34 (58.6%) in group 2, P = 0.02).

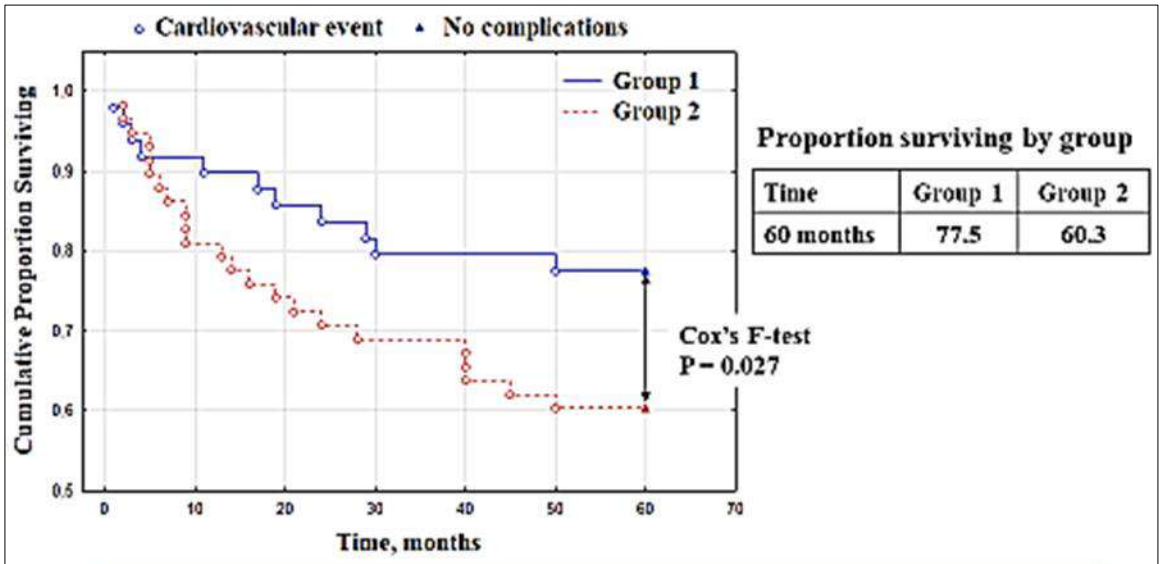
Another common comorbidity were lithogenic gallbladder disorders that were detected by ultrasonographic evidence of biliary sludge, presence of gallstones or prior cholecystectomy due to gallstone disease or calculous cholecystitis. Such abnormalities were found in 55.2% of patients with HTG comparing 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 just 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 more associated 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]. Although fibrates are recommended for patients with HTG who are at LDL-C goal [1], they may augment 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 promising results in case of non-alcoholic fatty liver disease [14].

Besides, more than half of female participants with HTG had prior hysterovariectomy (55.2% comparing with 19.0% in group 1, P = 0.018). Similar results were observed in the 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 control group [15].

However, the most important finding was 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 end-point (Figure 2). Cumulative proportion surviving in the end of observation were 77.5% and 60.3%, respectively (P = 0.027).




| Clinical outcomes after 5 years of observations | Group 1 | | Group 2 | |
|---|---|---|---|---|
| | 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 taken as a combined endpoint and number of events occurred in groups

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

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

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) comparing 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

Comparing with very high risk hypertensive patients without HTG, in 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 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 acute myocardial infarction, decompensated heart failure, stroke or death (39.6% vs. 22.4%, P = 0.027).

Further researches 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 interests

The authors of the study confirm that the research and publication of the results were not associated with any conflicts regarding commercial or financial relations, relations with organizations and/or individuals who may have been related to the study, and interrelations of coauthors of the article.

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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