VIA MEDICA

ORIGINAL PAPER

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The performance of triglyceride to high-density lipoprotein cholesterol ratio in acute coronary syndromes using a diagnostic decision tree

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Folia Medica Copernicana 2015;
Volume 3, Number 1, 13–19

ISSN 2300–5432

ABSTRACT

Background. Modern modeling techniques, including decision trees, may potentially provide accurate prediction and classification of outcomes, and support the process of clinical decision making. The objective of our study was to evaluate the performance of triglyceride to high-density lipoprotein (TG:HDL-C) ratio in acute coronary syndromes (ACS) presented using a decision tree analysis.

Methods. The initial study group consisted of 220 consecutive patients admitted to hospital within the first 6 hours from the onset of chest pain. All these patients met clinical criteria of ACS and were compared with 116 healthy volunteers in a case-control study. Serum was assayed on admission for cardiac troponin I, C-reactive protein, apolipoproteins ApoAI and ApoB, and lipid parameters. Atherogenic lipid ratios: TC:HDL:C, LDL-C:HDL:C and TG:HDL-C were calculated.

Results. ACS patients showed almost twice as high median values of TG:HDL-C as controls [2.77 (1.88–4.08) vs. 1.47 (0.99–2.08); $p < 0.0001$]. The TG:HDL-C ratio was significantly related to the positive history of coronary artery disease, age and lipid parameters, except for LDL-C. The TG:HDL-C ratio was, after age, the most powerful independent predictor and classifier of the occurrence of ACS with the optimal cutoff being 2.28. The performance of TG:HDL-C was superior to other lipid parameters and ratios, and enabled identification of the additional 6 subjects with ACS.

Conclusion. The TG:HDL-C ratio is a useful risk marker of the ACS occurrence. Further prospective studies are needed to confirm our findings and clarify the interaction between TG and HDL-C concentrations in ACS patients.

Key words: acute coronary syndrome, triglyceride to high-density lipoprotein cholesterol ratio, classification matrix, decision tree

Folia Medica Copernicana 2015; 3 (1): 13–19

Introduction

The identification and estimation of multiple risk factors are recommended by the guidelines for cardiovascular prevention and may support clinical decision making. In the past few decades, the cholesterol hypothesis has identified cholesterol as a major cause of atherosclerosis, and low-density lipoprotein cholesterol (LDL-C) has become the main goal for therapy. However, recently the population has become increasingly unhealthy, overweight or obese, with a growing number of adverse metabolic disorders, including insulin resistance, hypertension, metabolic syndrome, diabetes and coronary artery disease (CAD). Most of them are characterized by abnormalities of lipid metabolism, including atherogenic dyslipidemia with a special emphasis on so-called triglyceride to high-density lipoprotein axis disorders, consisting of high concentrations of triglycerides (TG) and low concentrations of high-density lipoprotein cholesterol (HDL-C). Despite the unquestionable success associated with statin therapy, a majority of statin-treated patients continue to

show the evidence of dyslipidemia. Moreover, all statin trials showed a substantial residual risk, even among patients who achieved LDL-C concentration below 70 mg/dL. Results of a meta-analysis on statin therapy showed that lowering LDL-C by 1 mmol/L reduces major coronary events by 23%, leaving an unaddressed cardiovascular residual risk of 77% [1, 2]. Subsequent studies indicated that aggressive lowering of LDL-C with maximal doses of statins does not eliminate cardiovascular risk, which was further reduced by only 22% [2]. This contributed to the intensification of actions aimed to clarify the mechanisms that cause lipid abnormalities, as well as better understanding of the role of other, beyond LDL-C, lipid risk factors for cardiovascular risk. Until recently, it was considered that elevated TG concentrations predict future coronary events in univariate analysis, but the impact was weakened after adjustment for other covariates which were strongly negatively correlated to TG, such as HDL-C [3]. This led to the reduction of the significance of TG role in the assessment of cardiovascular risk. However, over the past decade, evidence of the importance of TG:HDL-C abnormalities can be seen in several studies, which explained much of the pathophysiology of TG:HDL-C disorders. High TG concentrations can result in both low HDL-C and low LDL-C concentrations leading to a state in which the residual risk persists. A better understanding of lipoprotein-related residual risk with simultaneously better risk assessment strategy, regardless of LDL-C concentrations, should contribute to the improvement of patient care.

Modern modeling techniques, including decision trees, may potentially provide accurate prediction and classification of outcomes, and support the process of clinical decision making. The objective of our study was to evaluate the performance of TG:HDL-C in acute coronary syndromes presented using a decision tree analysis.

Material and methods

The study was designed as a case-control study. Consecutive patients were admitted, due to the initial diagnosis of acute coronary syndrome (ACS), to the Department of Cardiology and Internal Medicine at the University Hospital in Bydgoszcz within the first 6 hours from the onset of chest pain. The exclusion criteria were as follows: 1) chronic heart failure (New York Heart Association class II–IV); 2) acute heart failure (Killip class II–IV); 3) pulmonary embolism within 6 months preceding the enrollment; 4) creatinine concentration > 176.8 mmol/L; 5) ACS within 6 weeks preceding the enrollment; 6) the presence of features suggestive of an active inflammatory process on admission, and 7) therapy with steroids, immunosuppressive agents, and nonsteroidal anti-inflammatory drugs (excluding low doses of aspirin). Among 267 subjects who fulfilled the requirements of the study according to the inclusion and exclusion criteria, 47 patients were diagnosed with unspecified chest pain or other heart diseases and were excluded from further analysis. Therefore, the final study group consisted of 220 patients (91 females and 129 males, aged 64 ± 12 years). All these patients met clinical criteria of ACS. Electrocardiographic examination was performed on admission and thereafter if clinically indicated. Echocardiography, stress tests, and cardiac catheterization were performed if needed.

Clinically healthy volunteers (61 women and 55 men, aged 52 ± 9 years) with no evidence of present renal, metabolic or inflammatory disease, heart failure, and recent myocardial infarction served as controls. Baseline characteristics of study participants are presented in Table 1.

The study protocol was approved by the Bioethics Committee of Collegium Medicum in Bydgoszcz at the Nicolaus Copernicus University in Torun and written informed consent was obtained from all patients and controls.

Fasting venous blood samples from controls were collected in the morning. Venous blood samples were collected from patients on hospital admission within 6 hours of chest pain onset. Serum was assayed on admission for cardiac troponin I (cTnI) and lipid parameters (ARCHITECT ci8200, Abbott Diagnostics). Any increase of cTnI above 0.032 ng/mL (the 99th percentile for the healthy population measured with a 10% coefficient of variation) was considered a positive result. High-sensitivity C-reactive protein (CRP) was measured using the BN II System nephelometer (N High-Sensitivity CRP; Siemens Healthcare Diagnostics, Deerfield, IL, USA). Serum apolipoprotein AI (ApoAI) and apolipoprotein B (ApoB) concentrations were measured in samples stored frozen at –80°C for no longer than 6 months (ARCHITECT ci8200) and the ratio of ApoB : ApoAI was calculated. Serum total cholesterol (TC), TG, and HDL-C concentrations were used to calculate following lipid ratios: TC:HDL-C, LDL-C:HDL-C and TG:HDL-C. The optimal lipid cutoffs were defined as follows: TC < 200 mg/dL, LDL-C < 100 mg/dL, HDL-C > 50 mg/dL for women and > 40 mg/dL for men, and TG < 150 mg/dL according to the modified definition of the Third Report of the National Cholesterol Education Program [4]. TC:HDL-C < 4 and TG:HDL-C < 3 were regarded as optimal.

Statistical analysis

Basic statistical analysis

The patient data were expressed as mean ± standard deviation and median with 25th–75th percentiles

Table 1. Baseline characteristics of the study participants

Parameter	ACS patients n = 220	Control group n = 116	p
Age (years)	64.3 ± 12.1	52.1 ± 9.3	0.01
TC [mg/dL]	192 (159–232)	184 (165–197)	0.024
LDL-C [mg/dL]	123 (91–153)	108 (89–122)	0.002
HDL-C [mg/dL]	44.9 ± 12.1	56.1 ± 12.0	< 0.0001
non-HDL-C[mg/dL]	149 (120–180)	124 (108–137)	< 0.0001
TG [mg/dL]	116 (88–168)	81.5 (63–166.5)	< 0.0001
TC:HDL-C	4.43 (3.72–5.42)	3.23 (2.82–3.72)	< 0.0001
TG:HDL-C	2.77 (1.88–4.08)	1.47 (0.99–2.08)	< 0.0001
LDL-C:HDL-C	2.77 (2.16–3.55)	1.85 (1.56–2.27)	< 0,0001
ApoAI [g/L]	1.27 ± 0.24	1.41 ± 0.31	< 0.0001
ApoB [g/L]	0.81 (0.65–1.00)	0.72 (0.61–0.86)	0.0009
ApoB:ApoAI	0.64 (0.52–0.8)	0.51 (0.45–0.62)	< 0.0001
CRP [mg/L]	2.79 (1.12–6.08)	0.69 (0.36–1.35)	< 0.0001
BMI [kg/m^2]	26.8 (24.5–29.8)	24.4 (22.1–27.7)	0.014
Women	41% (91)	47% (55)	
Men	59% (129)	53% (61)	
Dyslipidemia	87% (191)	57% (66)	< 0.00001
Hypertension	74% (163)	20% (23)	< 0.00001
Diabetes mellitus	26% (57)	0	< 0.00001
Smoking	54% (119)	27% (31)	0.0001
Family history of premature CAD	35% (77)	26% (30)	0.29

TC — total cholesterol; LDL-C — low-density lipoprotein cholesterol; HDL-C — high-density lipoprotein cholesterol, TG — triglycerides; ApoAI — apolipoprotein A-I; ApoB — apolipoprotein B; BMI — body mass index; CRP — C-reactive protein; CAD — coronary artery disease

depending on the distribution. The Kolmogorov-Smirnov test was used to assess normality of distribution of the investigated parameters. Comparison between groups was performed by means of the Chi-square test for categorical variables, the unpaired Student's t-test for normally distributed variables, and the Mann-Whitney U-test for non-normally distributed variables. The association between variables was calculated with the Spearman and Kendall correlation coefficient where appropriate. P values lower than 0.05 were considered statistically significant.

Application of classification matrix, classification tree and patient dataset

A classification technique is a systematic approach to building classification models from an input data set. Each technique employs a learning algorithm to identify a model that best fits the relationship between the attribute set and class label of the input data. General approach for building a classification model is shown in Figure 1. The classification matrix gives estimates of the true classification and misclassification rules, and allows the evaluation of the performance of the designed model. Most classification algorithms seek models that attain the highest accuracy and, equivalently, the lowest error rate (ER) when applied to the test dataset.

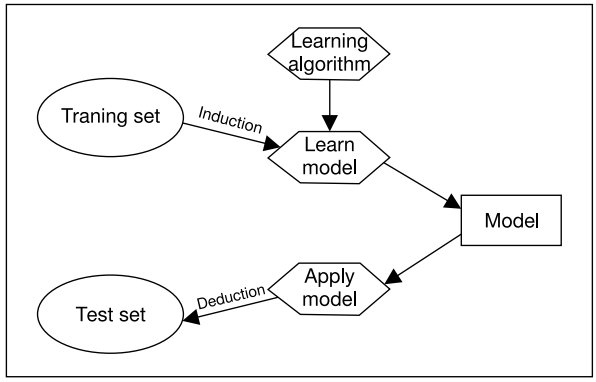

Figure 1. General approach for building a classification model

Table 2. Classification matrix in the diagnostic test for the occurrence of ACS

	Classification matrix		
Observed class	**Predicted class ACS = 0**	**Predicted class ACS = 1**	**Total in line**
ACS = 0	36	6	42
% in the column	100.00	4.55	
% in the line	85.71	14.29	
% in total	21.43	3.57	25.00
ACS = 1		126	126
% in the column	0.00	95.45	
% in the line	0.00	100.00	
% in total	0.00	75.00	75.00
Total number	36	132	168
Total %	21.43	78.57	

ACS — acute coronary syndrome

A tree-based classification and prediction modeling techniques use recursive partitioning to split the training records into segments with similar output variable values. The modeling starts by examining the input variables to find the best split, measured by the reduction on an impurity index that results from the split. The split defines two subgroups, each of which is subsequently split into two further subgroups, until the final criterion is met [5].

In our study, the initial patient dataset consisted of 220 subjects, but the observations with incomplete or missing data of at least 1 variable were dropped from the dataset. Therefore, the final ready to use patient dataset for our classification matrix and diagnostic decision tree consisted of 168 subjects. The model was optimized from a set of available clinical, laboratory and demographic variables, i.e. age, sex, body mass index (BMI), diabetes, hypertension, CRP, lipid profile and lipid ratios. Additionally, accuracy and ER for the model were calculated.

Statistical analysis, classification and decision tree modeling were performed using SPSS 17.0 software package (SPSS, Chicago, IL, USA).

Results

Baseline characteristics of the study participants, including lipid parameters, CRP, apolipoproteins concentrations and calculated lipid ratios constituting major cardiovascular risk factors are shown in Table 1. Patients with ACS had higher concentrations of TC, LDL-C, non-HDL-C, and TG, but lower levels of HDL-C and apoA-I compared with controls. They also presented significantly higher values of atherogenic ratios such as TC:HDL-C, LDL-C:HDL-C, apoB:apoA-I, and TG:HDL-C. Both groups were characterized by the presence of dyslipidemia, hypertension, and smoking. A quarter of ACS patients were diagnosed with type 2 diabetes.

In ACS patients, the univariate analysis showed direct relationships of TG:HDL-C with the positive family history of CAD (Kendall's tau = 0.13; $p < 0.01$) and age ($R = -0.34$; $p < 0.0001$). Among other variables, all the lipid parameters and ratios were significantly correlated with TG:HDL-C, except for LDL-C. There were no statistically significant relationships between the TG: HDL-C ratio and sex, diabetes, hypertension, BMI and CRP.

Evaluation of the performance of classification model for the occurrence of ACS was depicted in Table 2. The diagnostic model correctly classified all subjects as having ACS, and incorrectly classified 6 subjects. Therefore, we assumed that the diagnostic test based on the decision tree analysis correctly classified all ACS cases and allowed the identification of additional 6 subjects, who were incorrectly classified as non-ACS, as having ACS.

Finally, we developed a decision tree constituting a diagnostic test for the occurrence of ACS. Among available patient data, the most important classifiers in the model included: TC:HDL-C ratio (the optimal cutoff 3.27), age (the optimal cutoff 61.5 years), LDL:HDL-C ratio (the optimal cutoff 2.45), diabetes and, finally, TG:HDL-C ratio with the optimal cutoff 2.28 (Fig. 2). Performance metric calculated for this model included accuracy and the overall ER calculation, which were as follows: accuracy of 96.4% and ER of 0.03%.

Table 3 and Figure 3 summarize the importance of selected variables for the occurrence of ACS in the range of 1 to 0.05. The most important variables were: age, followed by TG:HDL-C, HDL-C and CRP. In contrast, the least important variables included family history of CAD, BMI and hypertension.

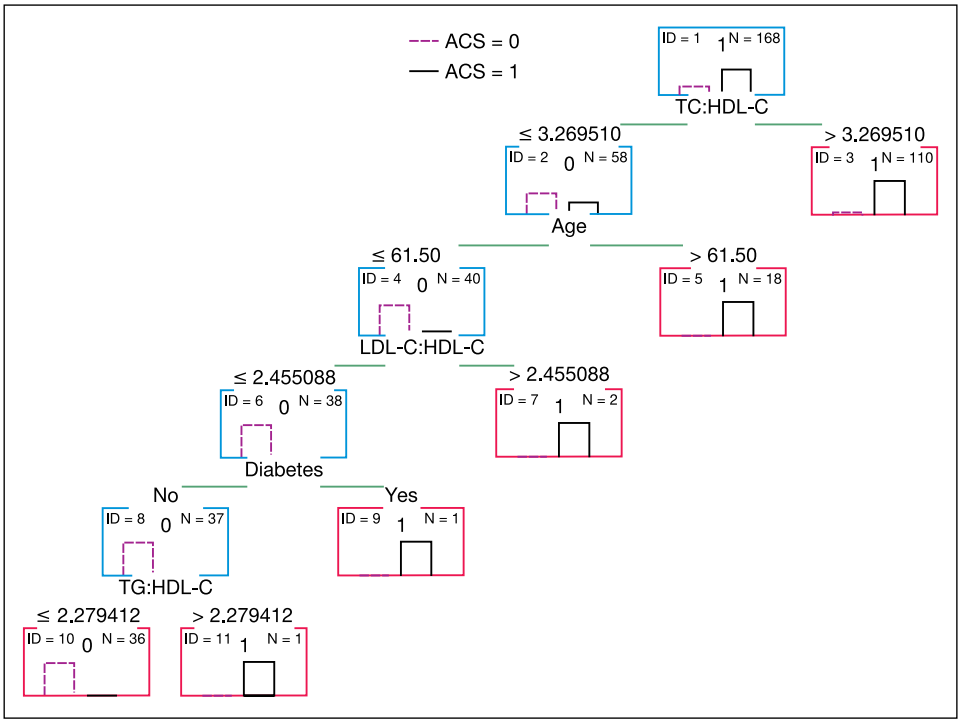

Figure 2. The diagnostic tree for evaluation of patients with ACS

ACS — acute coronary syndrome; LDL-C — low-density lipoprotein cholesterol; HDL-C — high-density lipoprotein cholesterol; TC — total cholesterol; TG — triglycerides

Table 3. Ranking of predictors in the evaluation of ACS patients

Variable	Ranking of predictors of ACS	
	Rank	Importance
Age	100	1.000
TG:HDL-C	83	0.831
HDL-C	72	0.717
CRP	57	0.569
Diabetes	56	0.559
TG	53	0.534
LDL:HDL-C	53	0.529
non-HDL-C	48	0.482
TC:HDL-C	47	0.473
ApoB:ApoAI	46	0.459
LDL-C	41	0.411
TC	38	0.377
ApoB	35	0.346
Sex	30	0.296
Smoking	29	0.292
ApoAI	24	0.244
Hypertension	18	0.184
BMI	12	0.117
Family history of premature CAD	5	0.052

ACS — acute coronary syndrome; TG — triglycerides; HDL-C — high-density lipoprotein cholesterol; CRP — C-reactive protein; LDL-C — low-density lipoprotein cholesterol; ApoAI — apolipoprotein A-I; ApoB — apolipoprotein B; BMI — body mass index; CAD — coronary artery disease

Discussion

We found the ratio of TG:HDL-C to be a powerful independent predictor and classifier of the occurrence of ACS. Moreover, the TG:HDL-C ratio was, after age, the second most important predictor of the occurrence of ACS, stronger than other traditional and lipid risk factors. Additionally, ACS patients showed almost twice as high median values of TG:HDL:C as controls. Importantly, both median TG:HDL-C value of 2.77 and TG:HDL-C classifier value of 2.28 in ACS patients were below the cutoff that characterizes a high risk (TG:HDL-C $\geq$ 4.0), but above the value considered as optimal (TG:HDL-C $<$ 2.00). The performance of TG:HDL-C in the diagnostic test presented by using decision tree analysis seems to be superior to other lipid parameters and ratios and enables the identification of the additional 6 subjects with ACS. The principal advantage of decision trees analysis is the lack of any presuppositions concerning the distribution of data. They are particularly useful in situations with correlated data. This is very important in the analysis of lipid parameters which, because of the common metabolic link, are strongly correlated with each other. Traditional statistical approach, even with the use of logistic regression, in this case is imperfect and may lead to an underestimation of the effects of certain lipid variables. In addition, on the basis of the decision trees it is easy to develop a variety of diagnostic standards or therapeutic procedures.

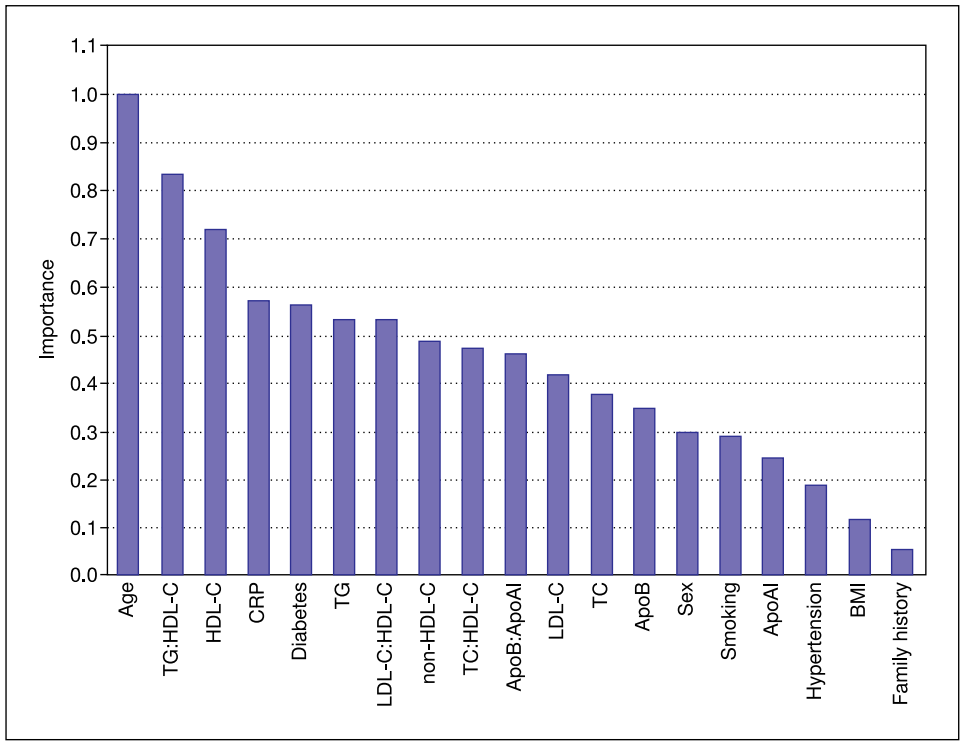

Figure 3. The importance of different classifiers in the evaluation of patients with acute coronary syndrome

TG — triglycerides; HDL-C — high-density lipoprotein cholesterol; CRP — C-reactive protein; LDL-C — low-density lipoprotein cholesterol; ApoAI — apolipoprotein A-I; ApoB — apolipoprotein B; TC — total cholesterol; BMI — body mass index

The TG:HDL-C ratio can easily be calculated from the lipid profile by dividing TG by HDL-C concentration. The TG:HDL-C ratio has been proposed by Gaziano et al., and recently has been proven to be a significant independent predictor of myocardial infarction, even stronger than other indices, including TC:HDL-C and LDL-C:HDL:C ratios. The initial data of Gaziano et al. suggest that TG:HDL-C ratio may be an important marker of abnormal TG metabolism, which may provide valuable additional information about the atherogenic potential of a lipid profile for the risk assessment [6]. These findings have recently been confirmed by others. Basically, the atherogenicity of the TG:HDL-C ratio results from higher TG and lower HDL-C concentrations. The state also known as residual risk is obviously shown by the presence of triglyceride-rich lipoproteins (TRL) found in fasting conditions in very low-density lipoproteins (VLDL) and in their remnants, and postprandial in chylomicrons and chylomicron remnants [7]. TRL particles are prone to undergo dynamic remodeling in the circulation which, in turn, results in the increased secretion of small, dense LDL during lipid exchange and lipolysis [7, 8]. Interestingly, it has been found that TG:HDL-C ratio can also predict the particle size of LDL and is associated with the presence of small dense LDL. Studies revealed that the elevated TG:HDL-C ratio (> 3.5) would suggest that the predominant LDL particle size is small in 80% of patients [9, 10].

In the Copenhagen General Population Study, lower concentrations of HDL-C were associated with higher concentrations of cholesterol and TRL remnants. In this study, 45% of men and 30% of women had TG ≥ 150 mg/dL and/or HDL-C < 40 mg/dL [11]. The ACS patients in our study were also characterized by lower concentrations of HDL-C and higher TG concentrations than healthy subjects, but their values were still within recommended ranges. The fact that subjects with higher TG:HDL-C ratio have a tendency to have higher TG > 100 mg/dL concentrations is indeed commonly known. Large epidemiological studies have clearly shown that both elevated TG and reduced HDL-C concentrations are associated with the increased cardiovascular risk. Whereas HDL-C displays athero- and vasculo-protective activity and was associated with a 22% reduction (per 1 SD increase by 0.38 mmol/L) in CAD risk, coronary risk increased by 37% (95% CI, 31–42%) per 1 SD increase in log TG [12]. Moreover, early reports from the Copenhagen Male Study showed that atherogenic dyslipidemia with the presence of high TG and low HDL-C concentrations was at least as powerful predictor of CAD as isolated high LDL-C concentrations in insulin-resistant subjects [11]. Therefore, TG:HDL-C ratio is also considered an independent marker of insulin resistance.

Interestingly, genetic studies provide potential evidence for cardiovascular risk associated with changes

in TG rather than HDL-C concentrations, which is not necessarily unexpected taking into account the complexity of metabolic pathways, especially for HDL-C [7].

We must acknowledge the important limitations of our study. We studied a selected, high-risk subset of patients who showed a higher prevalence of multiple risk factors than general population. Additionally, we did not include cardiac markers and electrocardiography, and did not take into account the use of statin therapy, which may weaken the inter-relationships between LDL-C and other lipid parameters.

In conclusion, our study indicates that the TG:HDL-C ratio is a useful risk marker of the ACS occurrence. Further prospective studies are needed to confirm our findings and clarify the interaction between TG and HDL-C concentrations in ACS patients.

Acknowledgments

The authors thank residents of the Department of Cardiology and Internal Medicine for their help in enrolling patients into the study. This study was partially supported by the Grant UMK 35/2009.

Conflict of interests

The authors declare that they have no conflict of interests.

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