Chapter 7

Lipoproteins Impact Increasing Cardiovascular Mortality

Jelena Umbrasiene, Ruta-Marija Babarskiene and Jone Vencloviene

Additional information is available at the end of the chapter

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1. Introduction

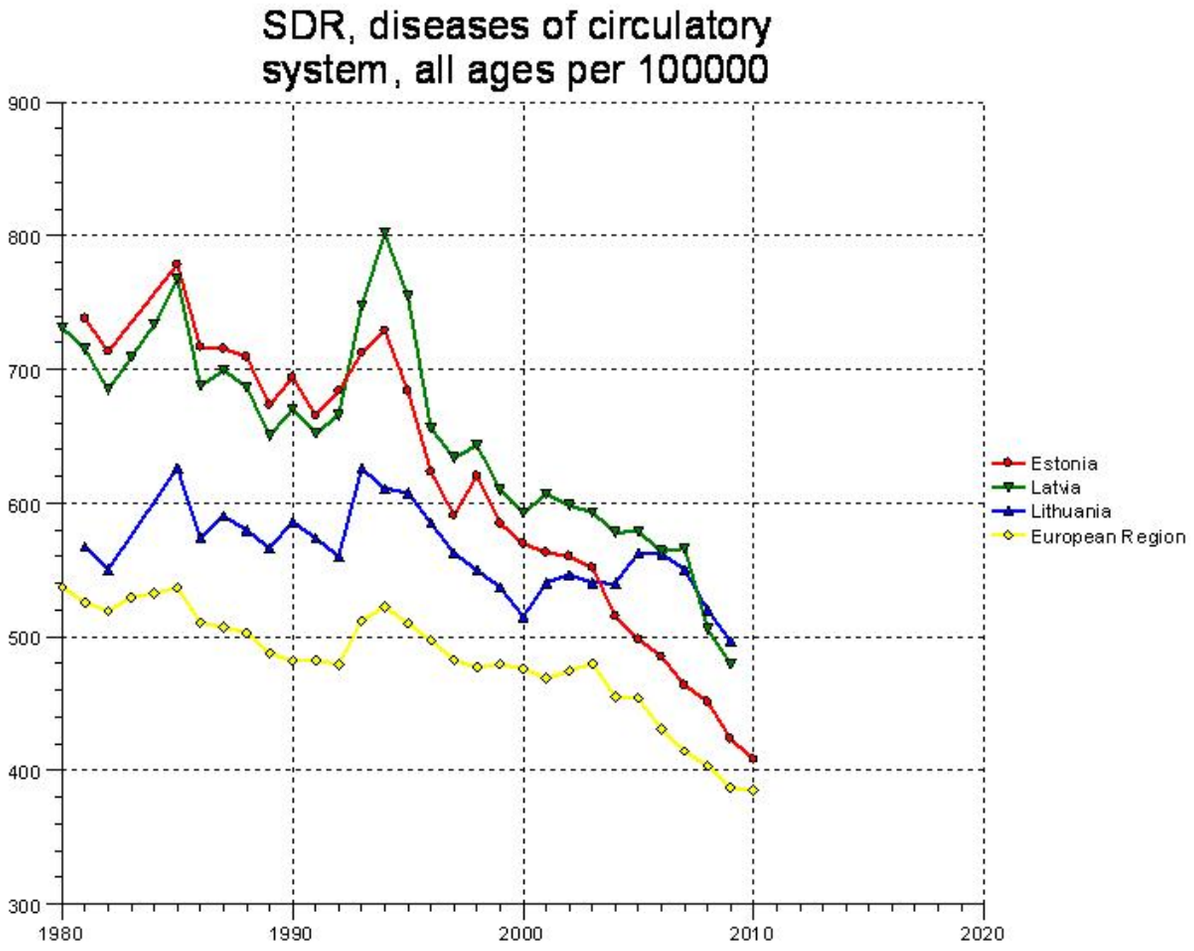
Cardiovascular diseases – the main result of the generalized atherosclerosis are the leading cause of global mortality all over the world [1,2]. The number of atherosclerotic diseases - an ischemic stroke, coronary heart disease and peripheral artery disease increases every year [1]. Possibly, due to increase in the population age, better health care and improved survival the prevalence of heart diseases is still so high [3]. The cardiovascular mortality in the most developed countries also is very high [2,3]. About half of all deaths occures due to cardiovascular diseases, it's an over 4,35 million deaths each year in the 53 member states of the World Health Organization European Region and more than 1,9 million deaths each year in the European Union [2]. Moreover there is a 35 billion euros damage due to working people production loss regarding to cardiovascular morbidity and mortality [2]. The cardiovascular mortality is still a problem not only in the European Union, but in the other developed countries as well. Atherosclerotic coronary artery disease was the most common cause of death in the United States in 2004. Men were more often affected, than women by a ratio of 4:1 and after age of 70 by ratio 1:1 [4]. In 2000 about 37 % of death in Canada were due to cardiovascular diseases [3]. They are still the main cause of mortality in Lithuania, as in the older Western European countries as well [5,6]. At the last decade, cardiovascular morbidity and mortality in Lithuania has not declined (Figure 1) [7,8].

In 2008 in Lithuania standartized cardiovascular mortality rate was 520,1 per 100 000 population (Figure 2) [8]. Although in the last years cardiovascular mortality has a tendency to decrease, it's still very high [7]. Lithuanian mortality from coronary artery disease rate in 2008 was 321,29 per 100 000 population (Figure 3) [7,8]. By the statistic data from the Lithuanian Institute of Hygiene, in 2011 56,3% of the people have died from cardiovascular

disease in Lithuania. In 2011, 20944 men and 20093 women have died, 47,7% and 62,7% due to coronary artery disease respectively [9].

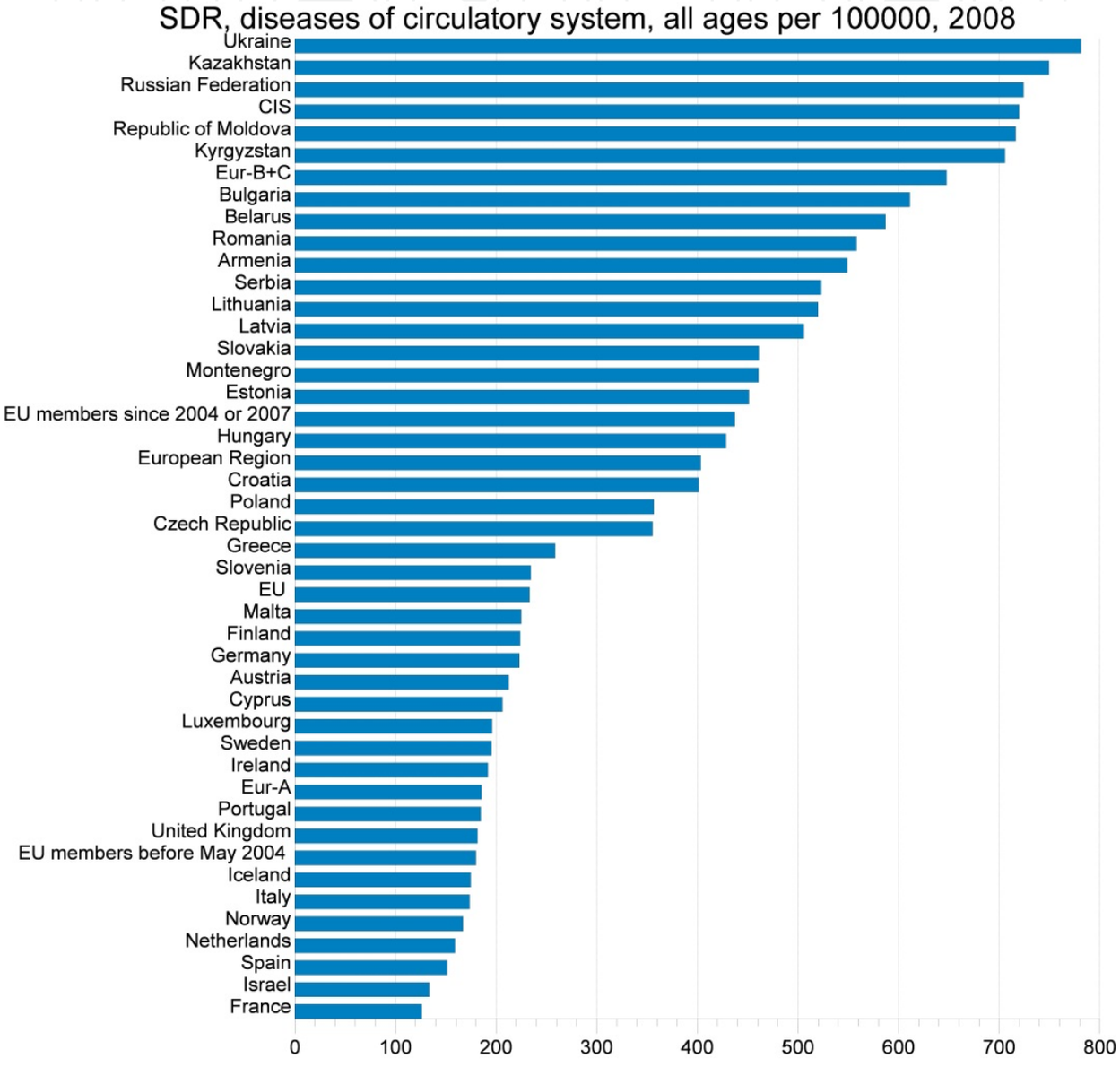
The main cardiovascular disease - coronary heart disease - highly associated with an increased cardiovascular mortality, hospitalisation and patients disability, significantly raising the cost of medical care [6]. In 2009 it was 4283,39 per 100 000 population hospital discharge for cardiovascular diseases and 1311,8 for coronary artery disease in Lithuania (Figure 4,5) [8].

In 2000 in Canada 7,3 billion dollars (17%) of total direct health care costs and 12,3 billion (14,5%) dollars of total indirect health care costs for all disease categories were attributed to cardiovascular diseases [3]. In the European Union, the economic cost of cardiovascular diseases in direct and indirect healthcare goes to 192 billion euros annually [1]. A total annual cost for person is vary from 50 euros in Malta to 600 euros in Germany, and 372 euros in average [2].



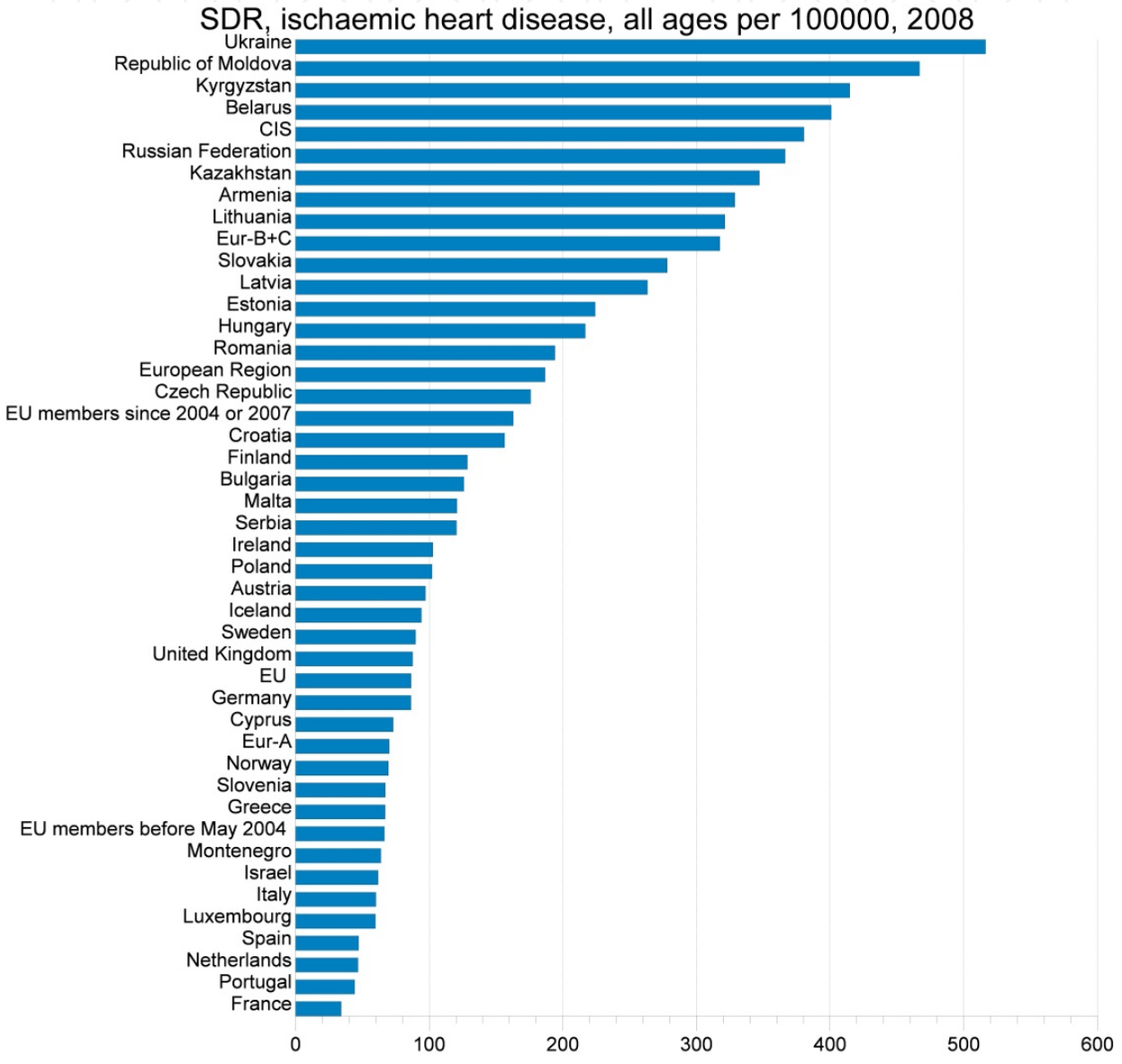
SDR – standartized death rate

Figure 1. Age standartized cardiovascular mortality rate for Baltic States and all European Region dynamic.



SDR – standartized death rate

Figure 2. Age standartized cardiovascular mortality rate per 100 000 population, 2008.



SDR – standartized death rate

Figure 3. Age standartized mortality rate for coronary artery disease per 100 000 population, 2008.

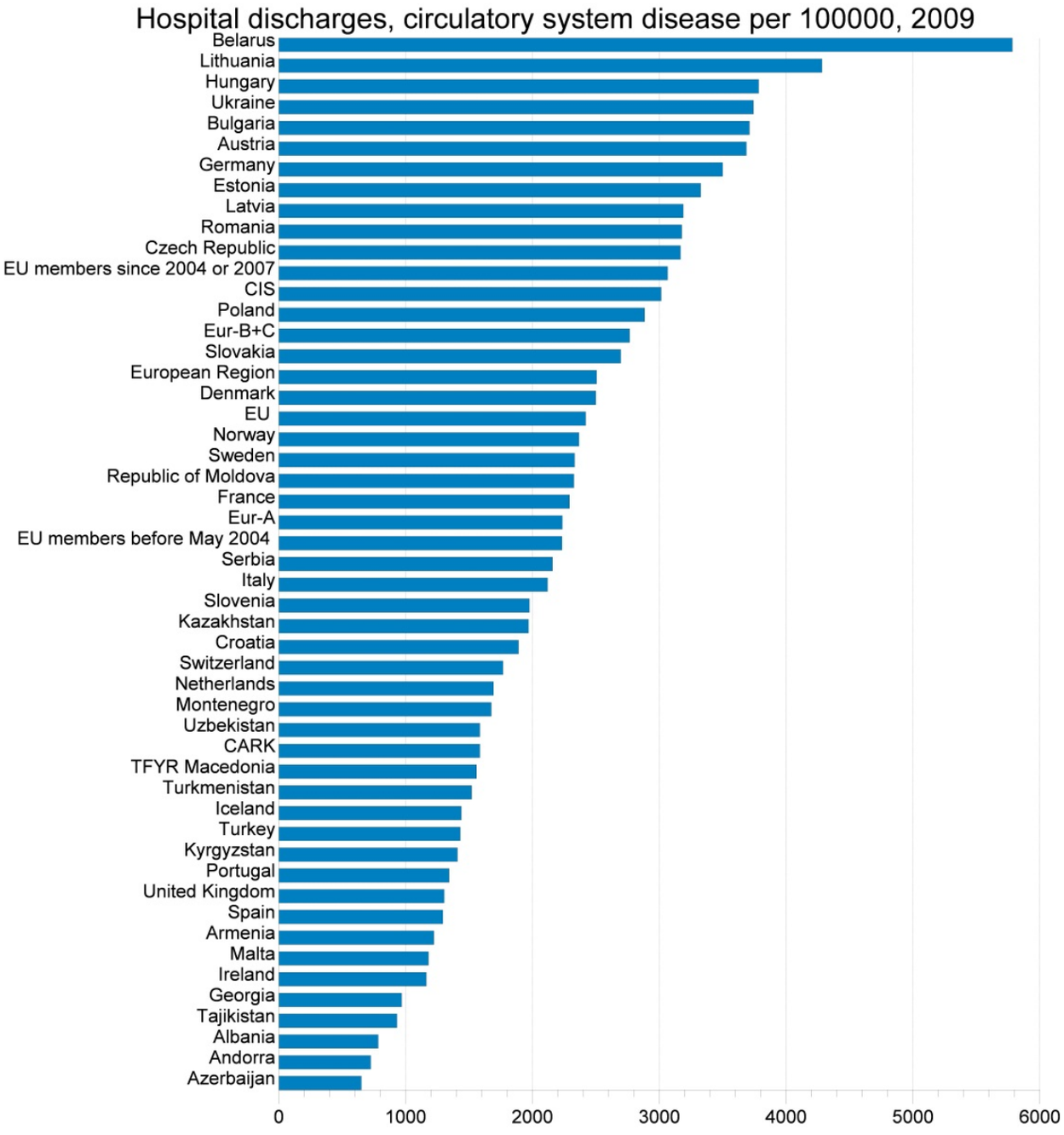


Figure 4. Hospital discharges for the patients with cardiovascular diseases in 2009, per 100 000 population.

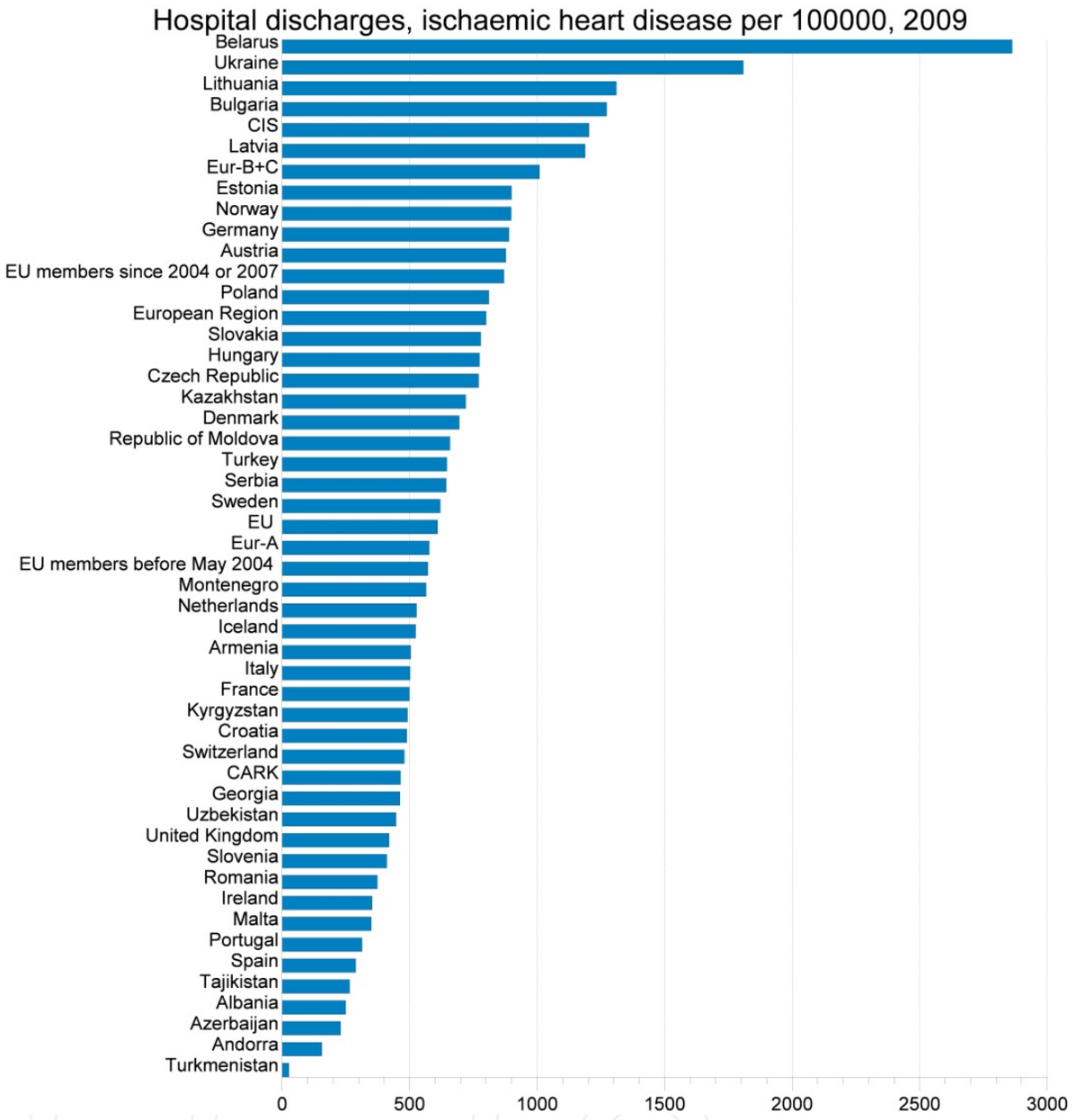


Figure 5. Hospital discharges for the patients with coronary artery disease in 2009, per 100 000 population.

Epidemiological studies have evaluated a number of important risk factors for coronary artery disease, such as positive family history, particulary in the age less than 40 for men, and 50 for women, age, male gender, blood lipids abnormalities, diabetes, hypertension, loss of physical activity, smoking and others, not so substantial (high sensitivity C-reactive protein, hyperfibrinogenemia etc.) [4,6,10-12]. Reducing one or more of these risk factors reduces the risk of major cardiac event accordingly [4]. There are a lot of evidence that lipoprotein disorder is the main pathogenesis of atherosclerosis. This relationship that was estimated century ago by Anitschkow is still important today [3,13]. Variuos epidemiological studies demonstrated a strong association between dyslipoproteinemia and coronary heart disease. There is a strong relation between serum cholesterol concentration

level and the coronary heart disease risk [14]. The Multiple Risk Factor Intervention Trial (MRFIT) in USA with 356222 men with different cardiovascular risk factors and 6-year follow-up period have shown that elevated total cholesterol blood concentration significantly increases cardiovascular risk [14,15]. In 2008, the authors published the report about the continuous follow-up for 25 years. The main finding was that total cholesterol is continuous and strong independent predictor for cardiovascular mortality. Estimated increased cardiovascular mortality risk at every total cholesterol level from 160 mg/dl (about 4,14 mmol/l) and higher [15]. Abnormal lipids metabolism or excessive intake of cholesterol especially with a genetic predisposition, initiates the atherosclerosis. A lot of clinical studies established total cholesterol and low density lipoprotein cholesterol are associated with a great risk of coronary heart disease. The reduce of total cholesterol by 10% decreasing the risk of ischemic heart disease by 25% within 5 years [16]. Low density lipoprotein cholesterol reduction not only decreases cardiovascular events, but reduce total mortality as well [3,17]. Furthermore, large randomized controlled clinical trials established the low density lipoprotein cholesterol lowering benefits [10]. It is proved, the reduce of low density lipoprotein cholesterol by 1 mmol/l, decreasing the risk of acute cardiac events by 20%, cardiovascular mortality by 22% [1,11,16-18]. Treatment of lipoproteins disorder also decrease the development of new lesion, regenerates endothelial function and signally reduce cardiovascular events in treated patients [4]. However, the data based on the National Health And Nutrition Examination Survey (NHANES) study from 2005-2008 have estimated that 71 million adults (33,5%) in the USA had elevated low density lipoprotein cholesterol level, but only 34 million (48,1%) were treated and 23 million (33,2%) had reached target low density lipoprotein value. Though, comparing this data to the data from NHANES study in 1999-2002, the number of people with elevated low density lipoprotein level treated with lipids-lowering medications increased from 28,4% to 48,1% between 1999-2002 and 2005-2008 periods. The prevalence of controled low density lipoprotein increased from 14,6% to 33,2% [17]. Although, statins significantly reduce low density lipoprotein cholesterol and coronary heart disease risk, substantial residual cardiovascular risk remains, even with very aggressive low density lipoprotein cholesterol values reduction [11,19,20]. However, atherosclerosis pathogenesis is multiple. It depends not only on low density lipoprotein cholesterol level, but also on genetic, environmental factors, infections, lifestyle factors and other diseases or condition [10-12]. More than a hundred different risk factors for atherosclerosis are estimated today. Although it is known many risk factors for coronary heart disease, the most of them are modifiable. Such as smoking cessation, treatment of dyslipidaemia, lowering of blood pressure can prevent the progression of atherosclerosis and major cardiovascular events [4]. One of the most important mechanisms of the atherosclerosis pathogenesis is Endothelial dysfunction [21]. In the early stages of atherosclerosis endothelian-dependent vasorelaxation disturbes due to oxidative stress and reduced nitric oxide bioavailability. Monocytes and T-lymphocytes adhesion occures. These inflammatory cells penetrate the cell wall, as well as lipid accumulation in the walls of blood vessels takes place. The inflammation and lipids accumulation make a plaque unstable, so it may occlude the vessel. Endothelial dysfunction is observed not only in the initial stage, but also in all other stages of atherosclerosis as well [21-23]. However, the main risk factors still

are male gender and older age (more common in women in menopause), heredity, hypertension, diabetes, smoking, stress, obesity, lack of physical activity, elevated low density lipoprotein cholesterol and total cholesterol and decrease high density lipoprotein cholesterol levels [6,10-12]. Numerous epidemiological studies have found reduced high density lipoprotein cholesterol as an independent risk factor for cardiovascular disease [24]. The Framingham study evaluated 43-44% increasing coronary events in patients with high density lipoprotein cholesterol < 40 mg/dL (1,03 mmol/l) [25]. Patients whose high density lipoprotein cholesterol less than 0,9 mmol/l (35 mg/dL) have 8 times higher risk of cardiovascular disease, versus those, whose high density lipoprotein cholesterol more than 1,68 mmol/l (65 mg/dL) [26]. Studies demonstrates that declined high density lipoprotein cholesterol levels are relatively common in general population. 16-18% of men and 3-6% of women have a high density lipoprotein cholesterol level less than 0,9 mmol/l (35 mg/dL) [20]. Moreover, the reduced high density lipoprotein cholesterol level is a component of the metabolic syndrome – the great predictor of high cardiovascular risk. Experimental studies have found high density lipoprotein cholesterol as a potential antiatherogenic by following characteristics. Estimated high density lipoprotein cholesterol facilitates reverse cholesterol transport and delivers cholesterol from the smooth muscles into hepatic cholesterol uptake. So, harmfull atherogenic cholesterol parts, such as low density lipoprotein cholesterol, are catabolized and neutralized [27-29]. High density lipoprotein cholesterol acts as an antioxidant, reducing vascular oxidative stress and has anti-inflammatory properties, reducing vascular inflammation due to atherosclerosis. There are evidence high density lipoprotein cholesterol has a vasoprotective effect, facilitates blood vessel relaxation, play an important role in the inhibition of white blood cells chemotaxis and adhesion. Also it is known about an anti-apoptotic effect of high density lipoprotein cholesterol on endothelial cells. High density lipoprotein cholesterol enhances the proliferation and migration of Endothelial cells and endothelial progenitor cells and thereby promotes the restoration of the endothelium's integrity. Finally, it has an antiplatelet/profibrinolitic effect, in this way reducing platelet aggregation and inactivating coagulation cascade [20,27-29]. Despite the evidence that reduced high density lipoprotein cholesterol is associated with an increased cardiovascular morbidity and mortality, the major guidelines in cardiology still do not recommend to initiate the treatment of dyslipidemia on high density lipoprotein cholesterol.

So, dyslipoproteinemia is a major risk factor for atherosclerosis and coronary artery disease. Its' proper recognition and management can significantly reduce cardiovascular and total mortality rates [12]. Follow the American Heart Association and the National Heart, Lung and Blood Institute and the Adult Treatment Panel III guidelines it is recommended to start treat from the low density lipoprotein cholesterol. Recent clinical studies provide supporting evidence for low density lipoprotein cholesterol target values of less than 2,5 mmol/l (< 100 mg/dl) for the prevention of coronary artery disease for the high cardiovascular risk patients and less thant 1,8 mmol/l (< 70 mg/dl) for the very high cardiovascular risk patients [1]. Studies demonstrate the significant decrease of atherosclerosis with aggressive reduction of low density lipoprotein cholesterol level in patients with coronary artery disease [3]. Only achieved target low density lipoprotein cholesterol value it is recommended to take care of

high density lipoprotein cholesterol. Studies evaluated, that high density lipoprotein cholesterol level more than 60 mg/dl (about 1,5 mmol/l) significantly reduce cardiovascular risk and can be named as „inverse risk factor" [21]. The target high density lipoprotein cholesterol is over 1,03 mmol/l (40 mg/dL) for men and more than 1,29 mmol/l (50 mg/dL) for women [20].

2. Lipoproteins disorder as a risk factor for cardiovascular mortality

Today there are more than one lipoproteins disorder classification. The Frederickson, Lees and Levy's one was based on the lipoprotein fraction after separation by electrophoresis. This classification recognized chylomicrons, very low density cholesterol and low density cholesterol. However, the main limitation of this classification, that it does not include high density lipoprotein cholesterol. That's why the World Health Organisation, the European Atherosclerosis Society and the National Cholesterol Education Program have classified lipoproteins disorder on the basis of the absolute plasma level of lipids (total cholesterol and trygliceride) and lipoprotein cholesterol level (low density lipoprotein cholesterol and high density lipoprotein cholesterol) [12,30]. This classification sustained on biochemical characteristics of lipoproteins and lipids. The plasma lipids do not circulate freely in plasma. They are bound to proteins and transported as macromolecular complexes called lipoproteins [24]. In these complexes lipids are surrounded by a stabilizing coat of phospholipid. There are five principal types of lipoprotein particles in the blood: very low density lipoproteins, intermediate density, low density, high density lipoproteins and chylomicrons. They are structurally different by electrophoretic mobility and density after separation in the ultracentrifuge and by the function [14,24]. The lipoprotein density depends on amount of fats contained within it [31].

Chylomicrons are the largest lipoproteins and synthesized in the small intestine from dietary fat and cholesterol [14,24,31]. They contain triglyceride from the intestine and a small amount of cholesterol. The main task of chylomicrons to transport the digestion products of dietary fat to the liver and peripheral tissue, where they are needed as a source of energy. In the circulation triglycerides are removed from chylomicrons via the action of lipoprotein lipase. If present in large amounts, such as after a fatty meal, chylomicrons cause the plasma to appear milky. Very low density lipoproteins are synthesized in the liver continuously and consists of triglyceride and cholesterol. Like chylomicrons they function primarily to distribute triglycerides to target sites such as adipose tissue and skeletal muscle where they are used for storage and energy [31]. It is the main body source of energy in prolonged fasting [14]. Like chylomicrons, they are removed due to lipoprotein lipase action. With removal of triglycerides and protein, very low density lipoproteins are converted to low density lipoproteins. High plasma levels of very low density lipoprotein cholesterol are to be found in familial hypertriglyceridaemia, diabetes mellitus, in people with a depressed thyroid function and in people with a high alcohol intake [31]. Intermediate density lipoproteins – one of the source of low density lipoproteins production. Last-mentioned are the main particles of lipids. They can deposit lipids into the

arterial wall and initiate atherosclerosis. Low density lipoprotein cholesterol are cholesterol-rich particles. About 70% of plasma cholesterol find in this form. Low density lipoprotein cholesterol have a main role in transporting the cholesterol manufactured in the liver to the tissues, where it is used. When low density lipoprotein cholesterol binds to low density lipoprotein cholesterol receptors on the cell surface, low density lipoprotein cholesterol is taken into the cell and broken down into free cholesterol and amino acids. Disorders involving a defect in or lack of low density lipoprotein cholesterol receptors are usually characterised by high plasma cholesterol levels. In the case of the inherited familial hypercholesterolemia the cholesterol excess cannot be cleared efficiently from the blood and therefore accumulates, caused coronary heart disease. And the last particles – high density lipoproteins are produced in liver and intestine. They are composed of 50% protein, with phospholipid and cholesterol as the remainder [31]. They transport lipids away from the periphery. The transfer of pro-atherogenic particles, such as very low density lipoproteins to the liver for the reverse cholesterol transport is one of the most important role of high density lipoprotein cholesterol. In this process harmful pro-atherogenic particles are transporting from the periphery to the liver for the reverse cholesterol transport and neutralizing [14,21]. It is well known low density lipoprotein cholesterol is one of the major factor for the development of atheroma. Atherosclerotic plaque consist of accumulated intracellular and extracellular lipids, smooth muscle cells, connective tissue, and glycosaminglycans.

There are two main hypotheses to explain the pathogenesis of atherosclerosis: the lipid hypothesis and the chronic endothelial injury hypothesis. Both of them are interrelated. The endothelial dysfunction is an initial stage of atherosclerosis, occures due to oxidative stress and sub-endothelial accumulation of lipids. Low density lipoprotein cholesterol undergo oxidation and become local cytotoxic. Macrophages migrate into the sub-endothelial space, take up lipids and become "foam" cells. The earliest detectable lesion of atherosclerosis is the fatty strip. This strip consists of foam cells full of lipids. As the process progress, the smooth muscle cells also migrate into the lesion. At this stage, the lesion may be hemodynamically insignificant. But endothelial dysfunction exists and it's ability to limit the entry of lipoproteins into the vessel is impaired [4]. So, the elevation of plasma low density lipoprotein cholesterol level results in penetration of low density lipoprotein cholesterol into the vessel wall, lipids accumulation in macrophages and smooth muscle cells. Endothelial injury produces loss of endothelium, adhesion of platelets to subendothelium, aggregation of platelets, chemotaxis of monocytes and T-cell lymphocytes, and release of growth factors that induce migration of smooth muscle cells from media to intima, where synthesize connective tissue and proteoglycans and forms a fibrous plaque. Low density lipoprotein cholesterol is cytotoxic and may cause endothelial injury and stimulate smooth muscle growth. Touched endothelial cell are functionally impaired and increase the uptake of low density lipoprotein cholesterol from plasma [24]. Growing atherosclerotic plaque may cause a severe stenosis that can progress to total arterial occlusion. Eventually the plaque may become calcified. Some plaques, reached in lipids and inflammatory cells, as macrophages, covered with a thin fibrous cap may undergo spontaneous rupture, resulting in cascade of events, stimulates thrombosis and ends in acute ischaemic event [4,24].

Hypercholesterolemia occures either from overproduction or defective clearance of very low density lipoprotein cholesterol or from increased conversion of very low density lipoprotein cholesterol to low density lipoprotein cholesterol. Overproduction of very low density lipoprotein cholesterol by liver may be caused by obesity, diabetes, alcohol consumption, nephrotic syndrome or genetic disorders. Each of this conditions can result in increased low density lipoprotein cholesterol and trygliceride levels. When dietary cholesterol reaches the liver, elevates intracellular cholesterol level. Due to this, low density lipoprotein cholesterol receptor synthesis is suppressed. This suppression occurs at the level of transcription of the low density lipoprotein cholesterol gene. A reduced number of receptors results in higher levels of plasma low density lipoprotein cholesterol and total cholesterol [24]. Today, it appears, that high density lipoprotein cholesterol assist in the mobilization of low density lipoprotein cholesterol [4]. Cardiovascular risk increases progressively with elevated of low density lipoprotein cholesterol and with a decrease in high density lipoprotein cholesterol level. Studies demonstrated that each decrease in high density lipoprotein cholesterol level by 1 mg/dl (0,0259 mmol/l) elevating cardiovascular risk by 2-3%. [20]. And contrarily, each increase in high density lipoprotein cholesterol level by 1 mg/dl (about 0,02 mol/l) lowering cardiovascular mortality by 6%, independently of low density lipoprotein cholesterol level [20,32]. Similarly, The Treating to New Target study evaluated high density lipoprotein cholesterol as a more significantly predictive for cardiovascular events comparing with low density lipoprotein cholesterol [21,33]. High density lipoprotein cholesterol is protective through multiple mechanisms. There are some new points in the high density lipoprotein cholesterol role and effects on atherosclerosis. Recently published studies showed the antooxidative role of high density lipoprotein cholesterol. Due to this effect the reduction of vascular oxidative stress is occured. It is thought, this can contribute to the atheroprotective effects. Supposedly, high density lipoprotein cholesterol decreases inflammatory process, stops the proliferation and migration of endothelial cells and has anti-apoptotic effects on them. All of this contributes to the anti-atherosclerotic effect [21]. High density lipoprotein cholesterol also affects the platelets function and haemostatic cascade [14].

The prevalence of hypercholesterolemia differ in the world. In 1996 in Taiwan 41,5% men and 19,6% of women had abnormal rates of plasma cholesterol [34]. In 1995 in Holand 19,2% of men and 12,4% of women have total cholesterol more than 6,5 mmol/l [35]. In 1999-2000 in Europe the European Action on Secondary Prevention through Intervention to Reduce Events (EUROASPIRE) study have been performed. The prevalence of high total cholesterol have been declined in Europe 1995-2000 from 86,2 till 58,8% In 2000 58,8% of the population have total cholesterol more than 5,0 mmol/l [36]. In 2006-2007 The European Society of Cardiology carried out the EUROASPIRE III survey in 76 medical centers in 22 European countries (Belgium, Bulgaria, Cyprus, Croatia, The Czech Republic, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Poland, the Netherlands, Romania, Russian Federation, Slovenia, Spain, Turkey and UK). The total 13935 participants with established coronary artery disease were reviewed and 8966 were interviewed 6 months after acute coronary event. 76,5% of all the patients had elevated total cholesterol and low density lipoprotein cholesterol. For 51% the total cholesterol more than 4,5 mmol/l was estimated and only for one half of them a total cholesterol goal (<4,5 mmol/l) was reached with lipid-lowering

medications, despite of the rather high rate of the statins prescription (80,7%). So, this study showed that one of the most important risk factor for cardiovascular mortality - dyslipoproteinemia control was inadequate and most of the patients did not achieve the targets defined in the guidelines [37]. By the data from MONICA project with 39 population from the 21 countries, in 2003 the main total cholesterol in Kaunas, Lithuania was near 6 mmol/l for men and 6,5 mmol/l for women. Females from Lithuania were at the top of all countries, whereas the men were about an average. 15 countries evaluated higher levels of total cholesterol for men [38]. One of the meta-analysis showed that the highest protective effect can be get treating high risk patients with very high total cholesterol level [39]. Regarding to the existing evidence on lipoproteins disorder, treatment and also due to increased cardiovascular mortality in Lithuania we started the clinical data. At this study we have evaluated independent risk factors for one year cardiovascular mortality for the patients with acute and chronic coronary syndromes. Lipoprotein disorder was one of the most important risk factor for one year cardiovascular mortality.

3. Methods

A total of 3268 patients with coronary heart disease who were selected for this study. The data was collected by a standardized questionnaire. A total of 1865 (728 women and 1137 men) with acute and chronic coronary heart disease, male and female, aged from 20 years till more than 80 years were reexamined after one year. Risk factors for coronary heart disease were evaluated. Lipoprotein disorder was definable as low density lipoprotein cholesterol level in twelve-hour fasting venous blood samples more than 3 mmol/l, total cholesterol level – more than 5,2 mmol/l, high density lipoprotein cholesterol level less than 1,2 mmol/l for women and less than 1,0 mmol/l for men. Due to medical history and data on admission patients were attributed to chronic or acute coronary syndrome. The myocardial infarction and unstable angina were attributed to acute coronary syndromes. Stable angina – to chronic coronary syndrome. Myocardial infarction was diagnosed according to the World Health Organisation guidelines: angina pain and equivalent, ischemic signs on ECG (Q wave, ST and T changes) and an increase in troponin I more than 0,05 mg/l. Unstable angina diagnosis confirmed with the angine syndrome, ischemic changes on the ECG without increasing enzymes in the blood and with angiography assessment of the coronary artery. Stable angina determined using a standard clinic, ECG, exercise test and angiography.

4. Statistical analysis

The statistical analysis was performed using SPSS (Statistical Package for Social Science) version 13 and Microsoft Office Excel 2003 statistical programs. Descriptive statistics was used for the quantitative data analysis. Categorical data have been summarized as frequencies and percentages, and for comparisons, chi-square test have been used. Univariate and multivariate logistic regression analysis was used for the risk assessment. One year mortality risk was evaluated by isolated and standardized odds ratios with 95% confidence interval (CI).

5. Results

The data from 1865 patients with chronic and acute coronary syndromes was analysed. For more than a half of the patients an acute coronary syndrome was diagnosed. The participants were mostly men (61%). 54,7% of the patients had a reduced level of high density lipoprotein cholesterol (less than 1,0 mmol/l for male, and less than 1,2 mmol/l for female), for about 32% an increased total cholesterol and low density lipoprotein cholesterol levels for each were evaluated. About 20,5% of the patients with decreased high density lipoprotein cholesterol level have elevated low density lipoprotein cholesterol level together. Nearly 90% of women with diagnosed dyslipidemia had a reduced high density lipoprotein cholesterol, whereas total cholesterol and low density lipoprotein cholesterol levels were elevated in about one-third of the females. The proportion in these atherogenic lipids in men was about 30% for everyone. 7,6% of the patients had died within one year. The one year cardiovascular mortality was similar for men and women, also for the patients with acute or chronic coronary syndrome. Nearly 22% of died patients had an increased levels of total cholesterol and low density lipoprotein cholesterol. For more than 67% of them the decrease of high density lipoprotein cholesterol was evaluated. The majority of the patients (50,5%) with acute coronary syndrome and more than 80% with stable angina had a reduced high density lipoprotein cholesterol (Table 1).

	High LDL[1] n(%)	**Low HDL[2] n(%)**	**High TC[3], n(%)**	**Total, n(%)**	**one-year CV mortality, n(%)**
Total	588 (31,5)	1021 (54,7)	594 (31,8)	1865 (100)	
Medical history					
Acute coronary syndrome	371(35,3)	531 (50,5)	359 (34,2)	1050(56,3)	90(8,6)
Chronic coronary syndrome	217(36,5)	490(82,5)	235(39,6)	815(43,6)	52(8,7)
Gender					
Female	241(33,1)	654(89,8)	264(36,2)	728(39)	55(7,5)
Male	347(30,5)	367(32,2)	330(29)	1137(61)	87(7,6)
Age groups					
< 70 years	419(35)	585(48,8)	433(36,2)	1197(64,2)	70(49,3)
70-80 years	144(25,6)	368(65,6)	136(24,2)	561(30,1)	56(39,4)
> 80 years	25(24,7)	63(62,4)	24(23,8)	101(5,4)	15(10,6)
One year CV mortality	31(21,8)	96(67,6)	31(21,8)	142(7,6)	

LDL- low density lipoprotein cholesterol, HDL – high density lipoprotein cholesterol, CV – cardiovascular; [1]>3,0 mmol/l, [2]< 1,0 for males; < 1,2 mmol/l for females, [3]> 5,2 mmol/l

Table 1. Patients baseline characteristics.

For the 34-40% of the patients elevated low density lipoprotein cholesterol and total cholesterol were diagnosed (Figure 6,7). Patients distribution due to age shows Figure 8.

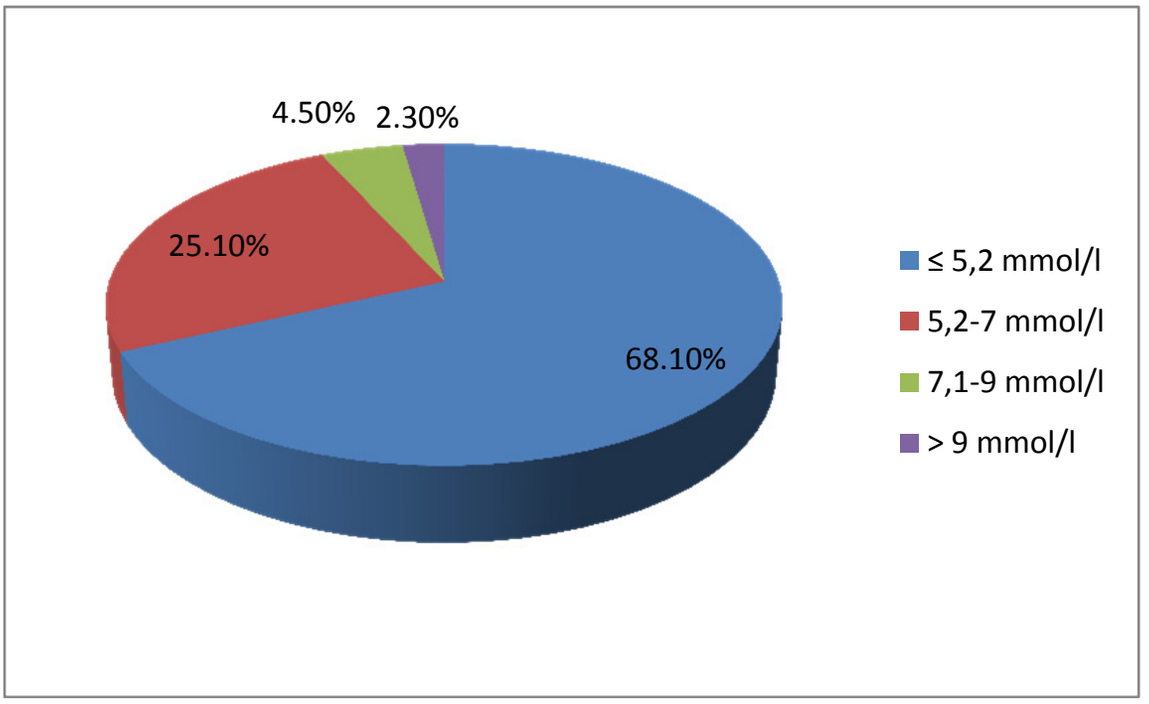


Figure 6. Part of the patients with different total cholesterol level.

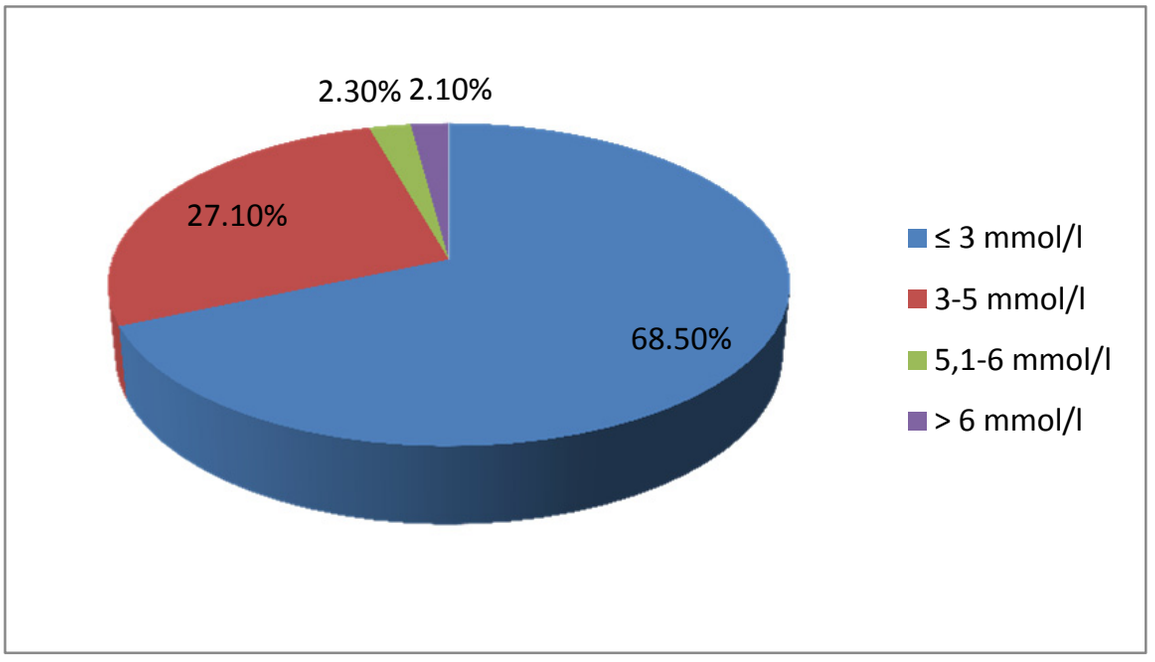


Figure 7. Part of the patients with different low density lipoprotein cholesterol level.

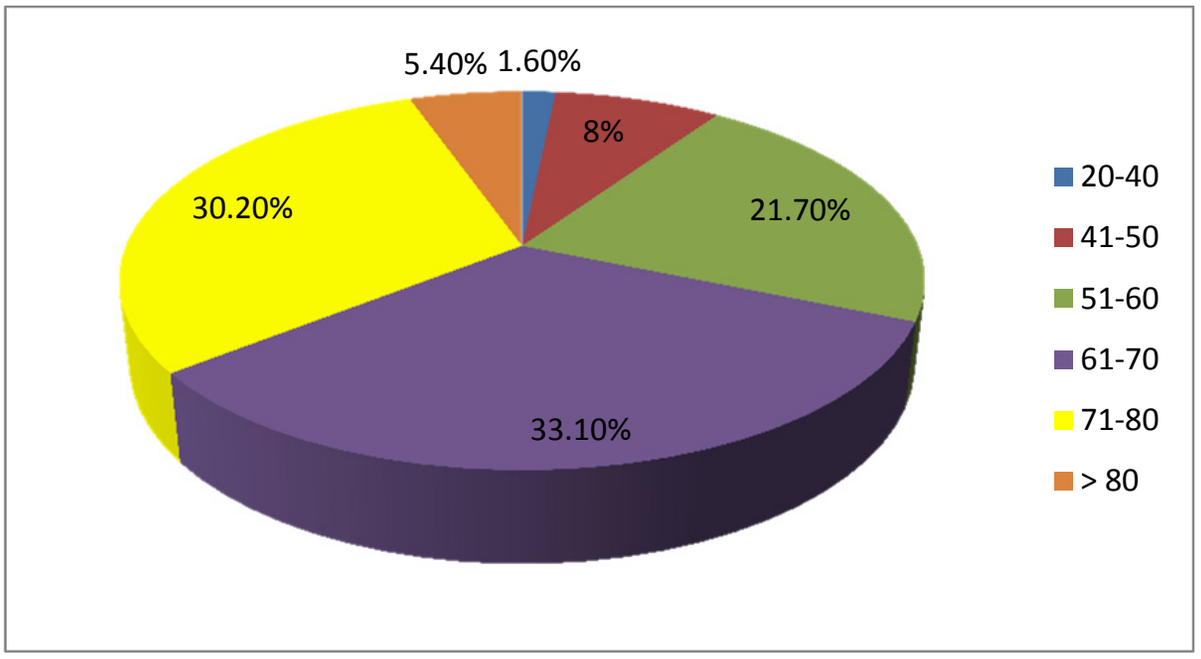


Figure 8. Patients distribution due to the age.

About 35-36% of the patients younger than 70 years, high total cholesterol and low density lipoprotein cholesterol levels were evaluated, the high density lipoprotein cholesterol have been decreased in nearly 49%. For the seniors (more than 70 years), the elevated total cholesterol and low density lipoprotein cholesterol were not so common (24-25% of the patients), but the reduced high density lipoprotein cholesterol was present more frequently (62-65%) (Table 1). Our data evaluated 1,8 times greater independent one year cardiovascular mortality risk for the patients with decreased high density lipoprotein cholesterol level (1,800, 95%CI 1,251-2,591, p=0,002). However, the assessment of the increased general values of the total cholesterol (more than 5,2 mmol/l) and low density lipoprotein cholesterol (more than 3,0 mmol/l) reduced mortality risk (0,575, 95%CI 0,382-0,868, p=0,008 and 0,585, 95%CI 0,388-0,882, p=0,01 respectively) (Table 2).

Risk factor	OR (95%CI)	p value
TC	0,575(0,382-0,868)	0,008
LDL	0,585 (0,388-0,882)	0,01
HDL	1,800 (1,251-2,591)	0,002

TC – total cholesterol, LDL- low density lipoprotein cholesterol, HDL – high density lipoprotein cholesterol

Table 2. Independent cardiovascular one year mortality rate.

Though, one year cardiovascular death risk elevates with the increase of these parameters (total cholesterol more than 9,0 mmol/l, low density lipoprotein cholesterol more than 6,0 mmol/l), although not significant (1,742, 95%CI 0,718-4,224, p=0,22 for total cholesterol more than 9,0 mmol/l and 1,167, 95%CI 0,408-3,339, p=0,773 for low density lipoprotein cholesterol more than 6,0 mmol/l). It is believed, the absence of the statistical significans due to small sampe size (Table 3).

Risk factor	OR (95%CI)	p value
TC		
5,2-7 mmol/l	0,465(0,286-0,759)	0,002
7,1-9 mmol/l	0,670(0,266-1,689)	0,396
> 9 mmol/l	1,742(0,718-4,224)	0,22
LDL		
3-5 mmol/l	0,524(0,333-0,825)	0,005
5,1-6 mmol/l	0,788(0,240-2,588)	0,694
> 6 mmol/l	1,167(0,408-3,339)	0,773
HDL		
< 1,0 for males; < 1,2 mmol/l for females	1,800(1,251-2,591)	0,002

TC – total cholesterol, LDL- low density lipoprotein cholesterol, HDL – high density lipoprotein cholesterol

Table 3. Independent cardiovascular one year mortality rate depending on lipoproteins level.

For the patients with acute coronary syndrome one year cardiovascular mortality rate insignificantly increases with the total cholesterol more than 9,0 mmol/l (2,578, 95%CI 0,931-7,136, p=0,068) and low density lipoprotein cholesterol more than 5 mmol/l (1,030, 95%CI 0,305-3,481, p=0,963 for the level of 5-6 mmol/l, and 2,023, 95%CI 0,668-6,130, p= 0,213 for the level more than 6,0 mmol/l). Simillary, high density lipoprotein cholesterol less than 1,0 mmol/l for men and less than 1,2 mmol/l for women increases one year cardiovascular mortality 1,4 times insignificantly (1,444, 95%CI 0,932-2,239, p=0,1) (Table 4).

Risk factor	OR (95%CI)	p value
TC		
>5,2 mmol/l	0,765(0,476-1,230)	0,269
5,2-7 mmol/l	0,633(0,364-1,102)	0,106
7,1-9 mmol/l	0,768(0,269-2,195)	0,623
> 9 mmol/l	2,578(0,931-7,136)	0,068
LDL		
> 3 mmol/l	0,724(0,451-1,164)	0,183
3-5 mmol/l	0,613(0,360-1,041)	0,07
5,1-6 mmol/l	1,030(0,305-3,481)	0,963
> 6 mmol/l	2,023(0,668-6,130)	0,213
HDL		
< 1,0 for males; < 1,2 mmol/l for females	1,444(0,932-2,239)	0,1

TC – total cholesterol, LDL- low density lipoprotein cholesterol, HDL – high density lipoprotein cholesterol

Table 4. Cardiovascular one year mortality rate for the patients with acute coronary syndrome depending on lipoproteins level.

For the patients with chronic coronary artery disease, only reduced high density lipoprotein cholesterol increased mortality risk, and this was great and significant (3,378, 95%CI 1,623-7,028, p= 0,001). It surprised the increase of the total cholesterol and low density lipoprotein

cholesterol reduced one year cardiovascular mortality (almost in all groups significantly, p<0,05) (Table 5).

Risk factor	OR (95%CI)	p value
TC		
>5,2 mmol/l	0,247(0,097-0,628)	0,003
5,2-7 mmol/l	0,183(0,056-0,595)	0,005
7,1-9 mmol/l	0,420(0,056-3,160)	0,005
> 9 mmol/l	0,667(0,087-5,124)	0,697
LDL		
> 3 mmol/l	0,276(0,108-0,705)	0,007
3-5 mmol/l	0,320(0,125-0,818)	0,017
5,1-6 mmol/l	-	-
> 6 mmol/l	-	-
HDL		
< 1,0 for males; < 1,2 mmol/l for females	3,378(1,623-7,028)	0,001

TC – total cholesterol, LDL- low density lipoprotein cholesterol, HDL – high density lipoprotein cholesterol

Table 5. Cardiovascular one year mortality rate for the patients with chronic coronary syndrome depending on lipoproteins level.

Both in men and women with reduced high density lipoprotein cholesterol elevated mortality risk was evaluated (2,044, 95%CI 0,622-6,716, p= 0,239 for women, and 2,303, 95%CI 1,483-3,577, p< 0,001 for men respectively). For females high total cholesterol (more than 9,0 mmol/l) and low density lipoprotein cholesterol (more than 6,0 mmol/l) insignificantly increased one-year cardiovascular mortality risk. For men, relevant total cholesterol level was more than 7,0 mmol/l and low density lipoprotein cholesterol more than 5,0 mmol/l, insignificantly (Table 6,7).

Risk factor	OR (95%CI)	p value
TC		
>5,2 mmol/l	0,236(0,105-0,530)	0
5,2-7 mmol/l	0,123(0,038-0,4)	0
7,1-9 mmol/l	0,263(0,035-1,963)	0,193
> 9 mmol/l	2,0(0,550-7,239)	0,292
LDL		
> 3 mmol/l	0,372(0,179-0,773)	0,008
3-5 mmol/l	0,283(0,119-0,674)	0,004
5,1-6 mmol/l	0,533(0,07-4,082)	0,544
> 6 mmol/l	1,743(0,375-8,106)	0,479
HDL		
< 1,0 for males; < 1,2 mmol/l for females	2,044(0,622-6,716)	0,239

TC – total cholesterol, LDL- low density lipoprotein cholesterol, HDL – high density lipoprotein cholesterol

Table 6. Cardiovascular one year mortality rate for females depending on lipoproteins level.

Risk factor	OR (95%CI)	p value
TC		
>5,2 mmol/l	0,926(0,568-1,510)	0
5,2-7 mmol/l	0,844(0,484-1,470)	0,548
7,1-9 mmol/l	1,050(0,366-3,017)	0,928
> 9 mmol/l	1,540(0,450-5,272)	0,491
LDL		
> 3 mmol/l	0,755(0,458-1,246)	0,008
3-5 mmol/l	0,722(0,421-1,239)	0,238
5,1-6 mmol/l	1,014(0,233-1,239)	0,985
> 6 mmol/l	0,892(0,207-3,852)	0,879
HDL		
< 1,0 for males; < 1,2 mmol/l for females	2,303(1,483-3,577)	0

TC – total cholesterol, LDL- low density lipoprotein cholesterol, HDL – high density lipoprotein cholesterol

Table 7. Cardiovascular one year mortality rate for males depending on lipoproteins level.

It was noticed, that a decrease in high density lipoprotein cholesterol – is an important and reliable cardiovascular mortality risk factor in middle-aged patients (40-60 years). For the 41-50 years patients the mortality risk increases nearly 5 times when high density lipoprotein cholesterol level declines less than 1,0 mmol/l for men, and less than 1,2 mmol/l for women (4,985, 95%CI 1,230-20,196, p<0,05). In the 51-60 year group the risk of death increases 2,5 times with a similar levels of high density lipoprotein cholesterol significantly (2,572, 95%CI 1,094-6,106, p< 0,05) and with a total cholesterol more than 5,2 mmol/l insignificantly (1,073, 95%CI 0,462-2,495, p=0,87). A similar trend for the high density lipoprotein cholesterol was evaluated for the elderly patients, without significance (due to small sample size) (Table 8,9,10).

Years	OR (95%CI)	p value
20-40		
41-50	0,591(0,147-2,383)	0,46
51-60	0,610(0,238-1,564)	0,303
61-70	0,581(0,258-1,312)	0,191
71-80	0,771(0,395-1,504)	0,445
>80	0,421(0,088-2,012)	0,279

Table 8. Cardiovascular one year mortality rate depending on age groups for the patients with increased low density lipoprotein cholesterol level.

Years	OR (95%CI)	p value
20-40	1,545(0,087-27,358)	0,767
41-50	4,985(1,230-20,196)	0,024
51-60	2,572(1,094-6,106)	0,032
61-70	1,155(0,568-2,347)	0,691
71-80	1,227(0,675-2,232)	0,502
>80	2,745(0,721-10,445)	0,139

Table 9. Cardiovascular one year mortality rate depending on age groups for the patients with decreased high density lipoprotein cholesterol level.

Years	OR (95% CI)	p value
20-40	2,111(0,118-37,722)	0,611
41-50	0,265(0,054-1,293)	0,1
51-60	1,073(0,462-2,495)	0,87
61-70	0,485(0,207-1,137)	0,096
71-80	0,654(0,321-1,334)	0,243
>80	0,448(0,094-2,142)	0,314

Table 10. Cardiovascular one year mortality rate depending on age groups for the patients with increased total cholesterol level.

6. Discussion

In the last decade, lack of evidence on low density lipoprotein cholesterol and high density lipoprotein cholesterol in the pathogenesis of coronary heart disease have appeared. Mostly long-term outcomes were evaluated by the previous studies on lipoprotein disorder. We decided to estimate impact of the dyslipoproteinemia to the one year survival. It is proved by another studies, that patients with very low high density lipoprotein cholesterol have much higher risk of severe cardiovascular event or cardiovascular death comparing with patients with normal high density lipoprotein cholesterol level. Lower high density lipoprotein cholesterol values are associated with a higher great cardiovascular events risk and a greater burden of atherosclerosis, even among the patients with reduced low density lipoprotein cholesterol level [33,40,41]. In another side, very low low density lipoprotein cholesterol level is a significant prognostic factor, improved survival for the patient with acute coronary syndrome and may be a target for the treatment. In this study first and foremost we found that reduced high density lipoprotein cholesterol are highly prevalent in a large cohort of the patients with coronary artery disease and tend to be associated with a significantly higher cardiovascular mortality risk. More than a half of the patients in our study had decreased high density lipoprotein cholesterol, and therefore the higher cardiovascular events and mortality risk, especially for the patients with stable angina. These data are similar to another studies [40]. Results from another studies showed that the prevalence of the elevated low density lipoprotein cholesterol increases with age [17]. By data from our

study it is not only the problem for the eldery patients. The prevalence of the impaired low density lipoprotein cholesterol by the gender was similar both for men and women and it was high for the patients with established coronary artery disease, taking notice that elevated low density lipoprotein cholesterol can be managed and controlled successfully with lifestyle changes, medications or a combination both of them. We have found that decreased high density lipoprotein cholesterol level is a significant independent risk factor for cardiovascular one year mortality. Interestingly, in another similar studies reduced high density lipoprotein cholesterol more often were found in young men. In our study 90% of females with coronary artery disease had a decreased high density lipoprotein cholesterol level. Also, insufficient high density lipoprotein cholesterol level more often have been found in eldery people. Although high density lipoprotein cholesterol less than 1,3 mmol/l for women has been widely considered as a cardiovascular risk factor, in the present study we selected a cutoff point of less than 1,2 mmol/l as a lowest high density lipoprotein cholesterol value that allowed us to identify those females at risk of cardiovascular one year mortality. It have been evaluated that about 20% of participants of our study had reduced high density lipoprotein cholesterol with elevated low density lipoprotein cholesterol level together. So, it is let to suspect, that one year cardiovascular mortality risk for them have to be much higher. There are a lot of evidence, that decreased high density lipoprotein cholesterol significantly increases cardiovascular mortality risk in stable patients. Also, there are some studies, showed that reduced high density lipoprotein cholesterol is associated with a higher risk of adverse outcomes [40]. Some reports on lipoproteins did not evaluated cardiovascular mortality due to acute or chronic ischaemic syndrome. Comparing acute coronary syndrome and chronic coronary artery disease patients we have been evaluated the more important role of total cholesterol and low density lipoprotein cholesterol on cardiovascular one year mortality for acute patients, though not significant. In contrast, high density lipoprotein cholesterol was strong independent risk factor both for acute (not significant) and chronic patients. Suprisingly, total cholesterol more than 5,2 mmol/l and low density lipoprotein cholesterol more than 3,0 mmol/l reduced one year mortality risk both for acute and chronic patients significantly. Additionally, the previous studies showed the increased mortality rate due to elevated low density lipoprotein cholsterol, have not comprehensively evaluated the impact of different low density lipoprotein cholesterol and high density lipoprotein cholesterol lipoproteins levels on cardiovascular mortality. Lehto and al. evaluated, that among 35-64 years females with acute myocardial infarction total cholesterol more that 8 mmol/l significantly increases reccurence cardiovascular disease risk [42]. It was a reason to search an impact of different levels of low density lipoprotein cholesterol and total cholesterol on cardiovascular mortality risk for men and women. Our hypothesis was confirmed, as it became clear, that one year cardiovascular mortality risk sharply rises when signally increased total cholesterol more than 9 mmol/l and low density lipoprotein cholesterol more than 6 mmol/l, especially in women. The future major research need to evaluate a different lipoprotein and total cholesterol levels impact in cardiovascular mortality, not only in short term, but in long-term outcomes as well. It seems, the highest levels of lipids, that could be attributed to hereditary

dyslipoproteinemia, may be very important predicting cardiovascular mortality rates and reducing a cardiovascular death risk. As it was find earlier, high density lipoprotein cholesterol more predictive for middle-aged men. Similarly, our study evaluated the more important role of decreased high density lipoprotein cholesterol, especially for 51-60 years men with the chronic coronary artery disease for one year cardiovascular mortality.

7. Conclusion

Lipoproteins disorder is the main factor for development of the atherosclerosis and predicts cardiovascular mortality. The most important findings from our data concerns the inverse relationship between the high density lipoprotein cholesterol and cardiovascular mortality rates. This association is characterized by a high degree of generality and strength.

Author details

Jelena Umbrasiene*
Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania,
Kaunas Region Cardiology Society, Kaunas, Lithuania,

Ruta-Marija Babarskiene
Kaunas Region Cardiology Society, Kaunas, Lithuania
Department of Cardiology, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania

Jone Vencloviene
Institute of Cardiology, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania,
Vytautas Magnus University, Kaunas, Lithuania

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* Corresponding Author

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