Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.elsevier.com/locate/medici

Original Research Article

Prevalence of dyslipidemia in statin-treated patients in the Baltic states (Estonia, Latvia, and Lithuania): Results of the Dyslipidemia International Study (DYSIS)

Margus Viigimaa [a,*], *Andrejs Erglis* [b], *Gustavs Latkovskis* [b], *Ene Mäeots* [c], *Žaneta Petrulionienė* [d], *Rimvydas Šlapikas* [e], *Anete Gocentiene* [f], *Peter Bramlage* [g], *Philippe Brudi* [h]

[a] *North Estonia Medical Centre, Tallinn University of Technology, Tallinn, Estonia*
[b] *Latvian Center of Cardiology, Pauls Stradins Clinical University Hospital, Riga, Latvia*
[c] *East Tallinn Central Hospital, Tallinn, Estonia*
[d] *Vilnius University Hospital Santariškių Klinikos, Vilnius, Lithuania*
[e] *Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania*
[f] *MSD UAB, Vilnius, Lithuania*
[g] *Institut für Pharmakologie und Präventive Medizin, Mahlow, Germany*
[h] *Merck & Co., Inc., Whitehouse Station, NJ, USA*

ARTICLE INFO

Article history:
Available online 10 June 2014

Keywords:
Cardiovascular disease
Dyslipidemia
Statins
Low-density lipoprotein cholesterol
High-density lipoprotein cholesterol
Triglycerides

ABSTRACT

Background and objective: The Baltic nations (Estonia, Latvia, and Lithuania) are profoundly affected by cardiovascular disease (CVD). Studies have indicated that patients may experience persistent dyslipidemia despite chronic statin treatment. Therefore, the aim of this study was to analyze the risk factors for dyslipidemia despite statin-treatment in a large dataset from the Baltic nations.

Material and methods: Patients in primary care centers across the Baltic nations were enrolled into the cross-sectional, observational Dyslipidemia International Study (DYSIS). Patients were ≥45 years old and had been treated with statins for at least three months. Patient characteristics and lipid measurements were used to determine variables contributing to dyslipidemia (abnormal low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], or total triglyceride [TG] values).

Results: We enrolled 1797 patients with a mean age of 66.1 years and 59.1% being female. Overall 63.4% had cardiovascular disease, 30.1% were diabetic and 77.8% at high risk for cardiovascular complications. LDL-C was not at target level for 80.7%; low HDL-C levels were

* *Corresponding author at*: North Estonia Medical Centre, Tallinn University of Technology, Ehitajate 5, 19086 Tallinn, Estonia.
E-mail address: margus.viigimaa@regionaalhaigla.ee (M. Viigimaa).

Peer review under responsibility of Lithuanian University of Health Sciences.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.medici.2014.05.003

observed for 26.0%, and elevated TG levels were found in 35.0% of all patients. Multivariate analyses indicated that a BMI ≥ 30 kg/m^2 (OR, 2.12; 95% CI, 1.45–3.08) and hypertension (OR, 2.43; 95% CI, 1.1 6–5.10) were strongly associated with dyslipidemia (involving all three lipids) during statin therapy while age ≥70 years (OR, 0.63; 95% CI, 0.42–0.94) and female gender (OR, 0.48; 95% CI, 0.33–0.68) conferred reduced risk.

Conclusions: Our findings indicate many statin-treated patients in Estonia, Latvia, and Lithuania did not meet target lipid levels and had a very high risk of CVD. Combating other well-known CVD risk factors such as obesity and hypertension is vital to reduce the exceptionally high riskfor CVD mortality seen in the Baltic nations.

1. Introduction

Cardiovascular disease (CVD) is known to be the leading cause of death and disability globally, and the World Health Organization (WHO) has estimated that it accounted for over 30% of the worldwide deaths in 2008. Moreover, by 2030, almost 25 million people are predicted to die as a result of CVD, involving mainly heart disease and stroke [1]. However, while many of these cardiovascular (CV)-related diseases are preventable, the rate of CVD continues to rise mainly due to inadequate treatment and preventive measures [2].

In the European Union (EU), CVD resulted in 36% of all deaths in 2010 (OECD, 2012). Thus, it is not surprising that the European Society of Cardiology (ESC) has published new guidelines that highlight the urgent need to improve CVD prevention [3]. Estonia, Latvia, and Lithuania (collectively known as the Baltics) are among the most profoundly CVD-affected countries within Europe [4], and 2010 Eurostat statistics indicated that the Baltic nations reported very high mortality rates for stroke compared to other countries in the EU, and comprised three out of the four countries (in addition to the Slovak Republic) with the highest rates of coronary heart disease-related mortality in Europe (OECD, 2012). Consistent with this, CVD led to a staggering 56%, 59%, and 55% of all deaths in Estonia, Latvia, and Lithuania (respectively) in 2008 [5–7]. Therefore, in the Baltic region, there is currently a vital need to implement preventative measures for combating well-known CVD risk factors, including hypertension, diabetes, smoking, and high cholesterol.

It is known that CV risk can be reduced through lipid-lowering therapies, including statins, with the primary goal of diminishing low-density lipoprotein cholesterol (LDL-C) [8–10]. Moreover, it was suggested that decreased high-density lipoprotein cholesterol (HDL-C) and elevated triglyceride (TG) levels might also contribute to CVD [11,12]. Nevertheless, several studies have indicated that patients under chronic statin therapy may experience persistent dyslipidemia, which can involve raised LDL-C, decreased HDL-C, and elevated TG levels [13–15]. The ongoing observational study, the Dyslipidemia International Study (DYSIS), has assessed the real-world effectiveness of lipid-lowering therapies in patients from various regions of the world in order to better understand CV risk factors [13,16–19].

Here, as part of DYSIS, we have analyzed dyslipidemia as defined by the European Society of Cardiology guidelines 2011 [20] in statin-treated patients within Estonia, Latvia, and Lithuania. The objectives of this study were to assess the prevalence of lipid abnormalities in patients receiving chronic statin treatment, and to identify specific demographic, lifestyle, and clinical risk factors that might contribute to persistent dyslipidemia. Data obtained during this study has contributed to our knowledge of CV risk, and can promote the advancement of programs and policies aimed at effectively preventing and treating CVD.

2. Material and methods

2.1. Study design and patients

DYSIS in the Baltics was an observational, cross-sectional, multicenter study conducted in Estonia, Latvia, and Lithuania between September 2011 and November 2012. Data for the study were collected by primary care physicians based on their willingness to participate distributed across participating countries using local-language case report forms and coordinated by the East Tallinn Central Hospital (Tallinn, Estonia), Clinical University Hospital (Riga, Latvia), Vilnius University Hospital Santariškių Klinikos (Vilnius, Lithuania) and Hospital of Lithuania University of Health Sciences Kauno Klinikos (Kaunas, Lithuania). Prior to study initiation, the relevant local ethical review committees approved study protocols and obtained informed consent for all patients. A total of 1797 patients (592, 600, and 605 from Estonia, Latvia, and Lithuania, respectively; 735 men and 1062 women in total) were enrolled. All patients were aged ≥45 years, treated with statins for at least three months, and had at least one fasting blood lipid profile available while on statins. The duration of statin treatment at the time of the fasting lipid profile was not specified and there is the potential that statin doses recorded at the survey where different from those at the time of the lipid profile.

2.2. Data collection

Patient demographic, lifestyle, and clinical characteristics were recorded. Lipid levels (total cholesterol, LDL-C, HDL-C and TGs) were obtained from the most recent blood samples taken within the previous 12 months. Additionally, the type and daily dose of statin being used by each patient was

recorded, as well as any information regarding other lipid-modifying therapies. Statin dose level was normalized using a potency calculation system as previously reported [21,22], where the potency of different statins was benchmarked against 6 simvastatin dose levels (5, 10, 20, 40, 80 and 160 mg/day), with potency scores ranging from 1 (5 mg/day simvastatin) to 6 (160 mg/day simvastatin).

Lifestyle related factors were defined as follows: current smoking was defined as a patient who regularly smokes (disregarding occasional smokers), but not those having smoked in the past. There was a question about physical activity with the potential answers sedentary life-style, more active life-style but no sports, and active life-style including regular exercise. Alcohol consumption was measured in units per week which equals to 10 mL by volume of 8 g by weight of pure alcohol.

2.3. Cardiovascular risk classification

The 2011 ESC guidelines were used to classify CV risk, LDL-C level treatment goals, and abnormalities in HDL-C/TG levels [20]. In these guidelines and the Guidelines on Cardiovascular Disease Prevention in Clinical Practice very high CV risk is defined as having CVD, diabetes, and/or an ESC Systematic Coronary Risk Evaluation (SCORE) risk of ≥10% (chronic kidney disease was not documented in DYSIS) [23]. Elevated LDL-C is defined as ≥1.8 mmol/L for patients with CVD, diabetes mellitus and/or a SCORE risk of ≥10%, and as ≥2.5 mmol/L and ≥3 mmol/L for patients with a SCORE risk of 5 to 9% and 1 to 4%, respectively and LDL-C reduction <50%. Low HDL-C levels are defined as < 1.0 mmol/L for men and <1.2 mmol/L for women. Elevated triglyceride levels are defined as being >1.7 mmol/L.

2.4. Statistical analysis

To estimate the sample size needed for the Baltic countries we assumed a prevalence of lipid abnormalities between 20 and 60% and a design effect of 20% (variance inflation due to cluster sampling design). We calculated that, within this range, a sample size of 1800 would be sufficient to estimate the prevalence with a given precision of ±2.5% (range of 95% confidence interval 5.0%). Furthermore we determined that this size guaranteed enough information for estimating the prevalence in smaller subgroups (representing one quarter or more of the population) with a precision of ±5.1% (range of 95% CI, 10.2%).

After data were collected at each of the primary sites, it was entered into a central web-based database housed and managed at the Institut für Herzinfarktforschung, Ludwigshafen, Germany. Real-time quality control (internal logic checks) occurred during web-based data entry. Continuous variables were presented as means with standard deviations or medians with 25th and 75th percentiles (interquartile range [IQR]) as appropriate. Categorical variables were reported as absolute numbers and percentages.

Associations of baseline variables with dyslipidemia (abnormal LDL-C, HDL-C, or TG values) were assessed using

Table 1 – Patients' characteristics, risk categories, and lipid parameters.

Characteristic	All patients (n = 1797)	Men (n = 735)	Women (n = 1062)
Age, mean (SD), years	66.1 (9.5)	64.3 (10.0)	67.4 (9.0)
Caucasian, %	99.9	99.9	100.0
Family history of premature CHD, %	33.1	32.9	33.2
Current smokers, %	10.7	18.1	5.6
Hypertension, %	87.4	85.4	88.8
Systolic BP, mean (SD), mm Hg	136.0 (15.2)	134.6 (14.6)	136.9 (15.6)
Diastolic BP, mean (SD), mm Hg	80.7 (9.1)	80.8 (9.4)	80.6 (9.0)
Waist circumference, mean (SD), cm	100.5 (13.7)	104.3 (12.1)	97.9 (14.1)
BMI, mean (SD), kg/m^2	30.5 (5.7)	29.9 (4.8)	31.0 (6.2)
BMI > 30 kg/m^2, %	48.8	44.5	51.8
CVD, %	63.4	75.1	55.4
Diabetes mellitus, %	30.1	29.8	30.3
Metabolic syndrome (IDF), %	66.3	64.0	67.9
ESC risk level (2011)*			
Very high risk patients, %	77.8	86.8	71.6
High risk patients, %	6.6	4.8	7.8
Moderate risk patients, %	13.1	8.3	16.5
Low risk patients, %	2.5	0.1	4.1
Lipids			
LDL-C, mean (SD), mmol/L	3.1 (1.2)	2.9 (1.1)	3.2 (1.2)
HDL-C, mean (SD), mmol/L	1.4 (0.4)	1.2 (0.4)	1.5 (0.4)
Total cholesterol, mean (SD), mmol/L	5.2 (1.4)	4.9 (1.3)	5.4 (1.4)
Triglycerides, median (IQR)	1.4 (1.0–2.0)	1.4 (1.0–2.1)	1.4 (1.0–1.9)
Blood glucose			
FBG, median (IQR), mmol/L	5.5 (5.1–6.2)	5.6 (5.1–6.2)	5.5 (5.0–6.1)
HbA1c diabetics, median (IQR), %	6.6 (6.1–7.3)	6.6 (6.1–7.4)	6.6 (6.0–7.2)

CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; BP, blood pressure; BMI, body mass index; CVD, cardiovascular disease; DM, diabetes mellitus; IDF, International Diabetes Federation; ESC, European Society of Cardiology; IQR, interquartile range.

multivariate logistic regression analysis with the following variables: age, sex, family history of premature coronary heart disease (CHD), smoking, physical activity, alcohol consumption (>2 units/week), body mass index (BMI) ≥30 kg/m^2, hypertension, diabetes mellitus, coronary heart disease, cerebrovascular disease, heart failure, peripheral artery disease, simvastatin equivalent dose of either 20 to 40 vs. 10 mg/day or >40 mg vs. 10 mg/day, and ezetimibe.

Kernel density estimation was used to analyze the distribution of total cholesterol, LDL-C, HDL-C, and triglyceride levels [24]. The value of a Kernel density and its slope at the lipid value equal to the ESC goal provides a crude indicator on how changes in lipid levels or changes in the treatment targets as per ESC guidelines would result in changing levels of lipid target achievement. Multiple logistic regression analyses with backward selection ($\alpha = 0.05$) were used to identify variables independently associated with abnormal LDL-C, HDL-C, and TG values. Two-tailed statistical comparisons were used ($P<0.05$ was significant), and patients lacking the appropriate lipid parameters were not included in the analyses. All analyses were performed using SAS v9.1 (SAS Institute Inc., USA).

3. Results

3.1. *Patient characteristics*

Patient characteristics, risk categories, and lipid parameters were collected by primary care physicians and are presented in Table 1. The mean age of all patients was 66.1 years; 59.1% were female, and 99.9% were Caucasian. Additionally, we found that 77.8% of the enrolled patients were at very high-risk for CV complications as determined through the ESC guidelines. Moreover, 63.4% of the individuals had a diagnosis of CVD, 30.1% were diabetic, and 66.3% were classified as having metabolic syndrome based on the International Diabetes Federation (IDF) definition. Also, a large number of patients (87.4%) were hypertensive, and 48.8% were obese (BMI ≥ 30 kg/m^2).

3.2. *Lipid-modifying treatments and statin potency*

Prior to enrollment in DYSIS, patients had been treated with various lipid-lowering therapies. Over half (64.8%) of the patients were on atorvastatin. In addition, 11.9% and 20.8% of patients were prescribed simvastatin and rosuvastatin, respectively, whereas fluvastatin, pravastatin, and lovastatin were used for 1.0%, 1.4%, and 0.1% of patients, respectively. Additional lipid lowering treatments were also given to a small percentage of patients. Moreover, the most frequently used statin dose potency was 4 for both very high-risk patients (44.8%) and non-very high-risk patients (45.4%), while the second most frequent dose potency was 3 (32.5% and 39.3% for very high-risk patients and non-very high-risk patients, respectively) (Fig. 1A and B).

3.3. *Lipid abnormalities*

Patient lipid abnormalities, according to the 2011 ESC guidelines, are depicted in Tables 2 and 3. Rates of lipid abnormalities

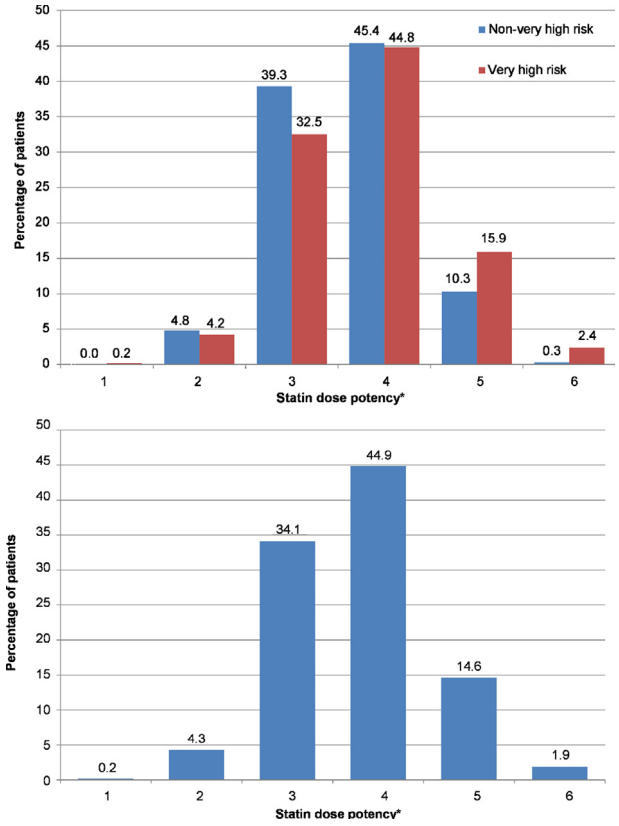

Fig. 1 – Statin dose potency according to patients' risk status (a) and overall (b) calculated according to Grundy et al. [21] and Roberts [22]. *Statin dose potency 1 is equivalent to simvastatin 5 mg/day, potency 2 is equivalent to simvastatin 10 mg/day, potency 3 is equivalent to simvastatin 20 mg/day, potency 4 is equivalent to simvastatin 40 mg/day, potency 5 is equivalent to simvastatin 80 mg/day, and potency 6 is equivalent to simvastatin ≥ 160 mg/day.

were comparable whether we analyzed patients with a total lipid profile or all patients. Importantly, LDL-C was not at target level for 80.7% of all patients analyzed. Moreover, when the patients were divided into subgroups based on very high-, high-, and moderate-risk for CVD, we found a corresponding decrease in the percentage of individuals off target for LDL-C levels (86.5%, 79.5%, and 62.7%, respectively). Low HDL-C levels were observed for 26.0% of all patients, and elevated TG levels were found in 35.0% of all patients.

We next performed a sub-analysis of lipid abnormalities for only very high-risk patients (1398 of all patients), and found that 365 of them had both CVD and diabetes mellitus (Table 3). Of these patients, 85.3% displayed off target LDL-C levels, 37.5% showed low HDL-C levels, and 42.8% had elevated TG levels. Furthermore, 82 of these very high-risk patients were found to have a SCORE ≥ 10%, and almost all of them (96.3%) did not reach target LDL-C levels. Interestingly, kernel density curves illustrated that the very high-risk group showed slightly lower overall LDL-C levels than non-very high-risk patients. Moreover, women maintained higher overall HDL-C levels than men in both the very high- and non-very high-risk

Table 2 – Lipid abnormalities according to the European Society of Cardiology guidelines (2011).

Variable	All patients (*n* = 1638)	Very high risk (*n* = 185)	High risk (*n* = 103)	Moderate risk (*n* = 209)	Low risk (*n* = 41)
LDL-C not at target[a]	80.8	86.2	80.6	63.2	...
Low HDL-C, mmol/L (<1.0 [men]/1.2 [women])	26.2	27.6	19.4	21.1	24.4
Elevated TG (>1.7 mmol/L)	35.1	35.4	31.1	37.3	24.4
All patients	(*n* = 1797)	(*n* = 1398)	(*n* = 118)	(*n* = 236)	(*n* = 45)
LDL-C not at target[a,b]	80.7	86.5	79.5	62.7	...
Low HDL- C, mmol/L (<1.0 [men]/1.2 [women])[b]	26.0	27.5	18.9	20.9	23.8
Elevated TG (>1.7 mmol/L)[c]	35.0	35.2	30.5	37.5	24.4

Values are percentage.
LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, total triglyceride.
[a] Data on 1781 patients were available.
[b] Data on 1696 patients were available.
[c] Data on 1679 patients were available.
Ellipsis indicates that in the ESC 2011 guidelines, no LDL-C goal was specified for the low-risk group.

groups, while TG levels were similar between the two risk groups (Fig. 2).

Distributions of single and multiple combined lipid abnormalities for our study are shown in Fig. 3A–F. In non-very high-risk and very high-risk patients displaying at least one lipid abnormality, 10.2% and 12.3% (respectively) had all three of the lipid irregularities (Fig. 3A and B). However, after including those patients without lipid abnormalities into these analyses, the proportions of patients with all three of the lipid irregularities were 7.6% and 11.4% for the two risk groups, respectively (Fig. 3C and D). Finally, in a combined analysis of all patients we found that 89.2% of patients displayed at least one lipid abnormality, while 10.8% of statin-treated patients were normal for all lipid parameters. Of those displaying at least one lipid abnormality, 11.9% showed all three of the lipid abnormalities (Fig. 3E and F). Also of note, very high-risk patients with at least one lipid abnormality showed an increased rate of LDL-C not at goal combined with low HDL-C compared to the non-very high-risk group (11.9% vs. 6.8%, respectively) (Fig. 3A and B). Interestingly, the opposite was true for the combination of low HDL-C and elevated TGs, which occurred more than twice as often in non-very high-risk patients (5.3% vs. 2.1%) (Fig. 3A and B).

3.4. *Variables independently associated with dyslipidemia*

Table 4 displays the results of multivariate logistical regression analysis, which identified several variables independently associated with abnormal LDL-C, HDL-C, and TG levels. LDL-C levels not at goal was positively associated with female gender, family history of CHD, sedentary lifestyle, alcohol consumption (>2 units/week), while age ≥70 years, diabetes mellitus, heart failure and high (80 mg/day) dose simvastatin (compared to low dose) had a negative association. Those positively independently associated with low HDL-C levels included those with BMI ≥ 30 kg/m^2, and diabetes mellitus while female gender and alcohol consumption were negatively associated. Elevated TG levels were associated with alcohol consumption, a BMI ≥ 30 kg/m^2, and diabetes mellitus. Importantly, a BMI ≥ 30 kg/m^2 and hypertension were among those

Table 3 – Lipid abnormalities according to the European Society of Cardiology guidelines (2011) in very-high risk patients.

Patients with total lipid profile	CVD + DM (*n* = 326)	CVD (w/o DM) (*n* = 729)	DM (w/o CVD) (*n* = 127)	SCORE ≥ 10% (*n* = 73)
LDL-C ≥ 1.8 mmol/L and LDL-reduction <50%	85.0	85.3	88.5	95.9
Low HDL-C (<1.0 [men]/1.2 [women] mmol/L)	37.1	24.6	28.0	15.1
Elevated TG (>1.7 mmol/L)	43.3	30.5	43.9	31.5
All patients	(*n* = 365)	(*n* = 775)	(*n* = 176)	(*n* = 82)
LDL-C ≥ 1.8 mmol/L and LDL-reduction <50%[a]	85.3	85.6	88.3	96.3
Low HDL-C (<1.0 [men]/1.2 [women] mmol/L)[b]	37.5	24.2	28.6	14.1
Elevated TG (>1.7 mmol/L)[c]	42.8	30.2	44.5	30.7

Values are percentage.
CVD, cardiovascular disease; DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, total triglyceride.
[a] Data on 1386 patients were available.
[b] Data on 1323 patients were available.
[c] Data on 1317 patients were available.

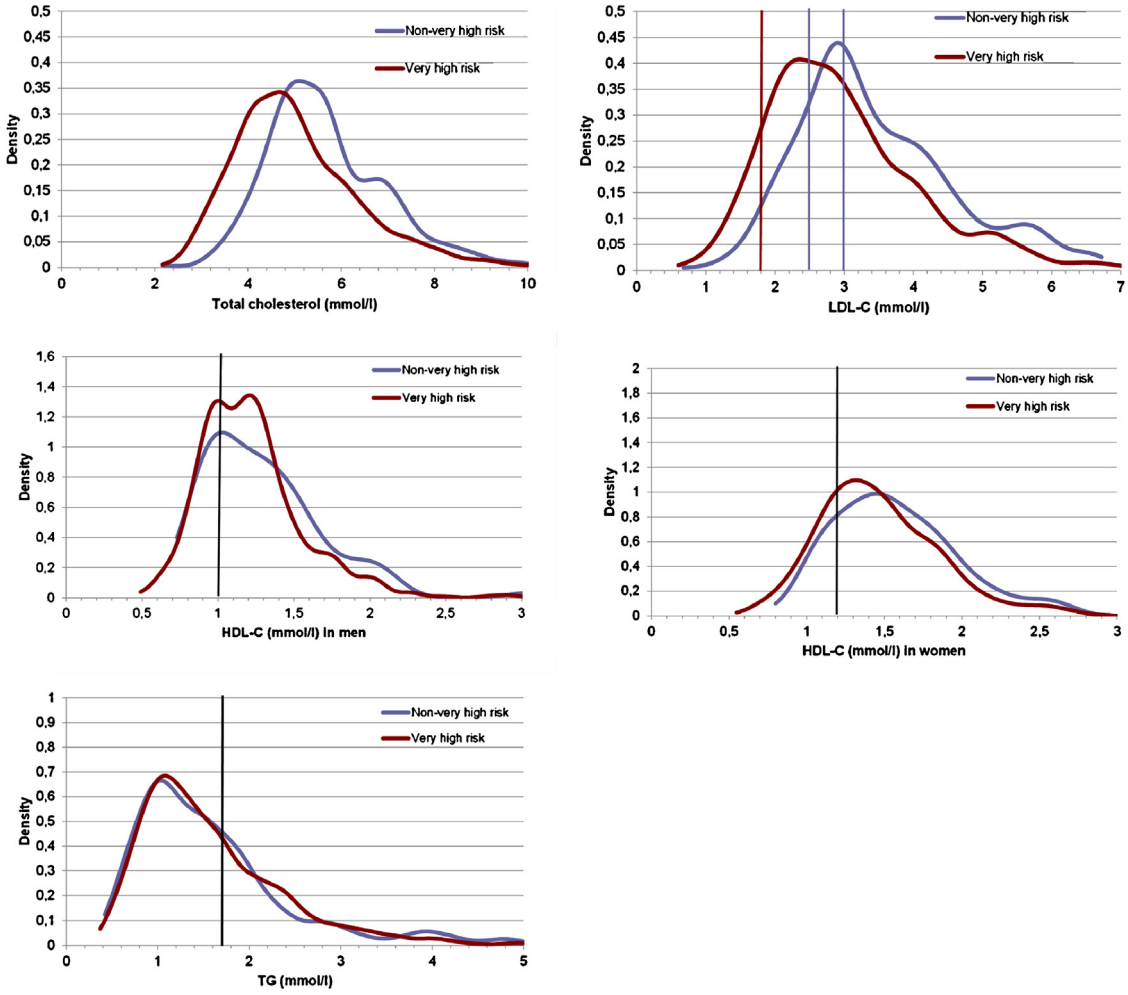

Fig. 2 – Kernel density curves of lipids. Vertical lines mark the cut point according to the European Society of Cardiology guidelines (2011).

Table 4 – Factors independently associated with low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride abnormalities: results of multivariable logistic regression.

Factor	LDL-C not at target[a] (≥1.8/2.5/3.0 mmol/L)	Low HDL-C[a] (<1.0 [m]/1.2 [w] mmol/L)	Elevated TG[a] (>1.7 mmol/L)	LDL-C not at target and low HDL-C and elevated TG[a]
Age ≥ 70 years	0.79 (0.64–0.97)	NS	0.62 (0.50–0.78)	0.63 (0.42–0.94)
Female	1.26 (1.02–1.55)	0.66 (0.47–0.90)	NS	0.48 (0.33–0.68)
Family Hx of premature CHD	1.30 (1.05–1.60)	NS	NS	NS
Sedentary lifestyle	1.27 (1.03–1.56)	NS	NS	NS
Smoking	NS	NS	NS	NS
Alcohol consumption > 2 units/week	1.54 (1.15–2.05)	0.66 (0.47–0.90)	1.65 (1.25–2.18)	NS
BMI ≥ 30 kg/m^2 (obesity)	NS	1.97 (1.55–2.49)	2.63 (2.11–3.26)	2.12 (1.45–3.08)
Diabetes mellitus	0.76 (0.61–0.94)	1.53 (1.20–1.95)	1.36 (1.08–1.71)	NS
Coronary heart disease	NS	NS	NS	NS
Hypertension	NS	NS	NS	2.43 (1.16–5.10)
Heart failure	0.77 (0.63–0.95)	NS	NS	NS
Simvastatin >80 vs. 10 mg/day	0.71 (0.55–0.93)	NS	NS	NS
Ezetimibe	NS	NS	NS	NS

Values are odds ratio (95% CI). Backward selection (alpha = 0.05) was done.
LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, total triglyceride; CHD, coronary heart disease; BMI, body mass index; m, men; w, women; NS, not significant; OR, odds ratio, CI, confidence interval.
[a] Models contained the following variables: age, sex, first-grade family history of premature CVD, smoking, sedentary lifestyle, alcohol consumption > 2 units/week, BMI ≥ 30 kg/m^2 (obesity), diabetes mellitus, coronary heart disease, cerebrovascular disease, heart failure, peripheral artery disease, hypertension, 20–40 vs. 10 mg/day simvastatin equivalent, ≥80 vs. 10 mg/day simvastatin equivalent, ezetimibe.

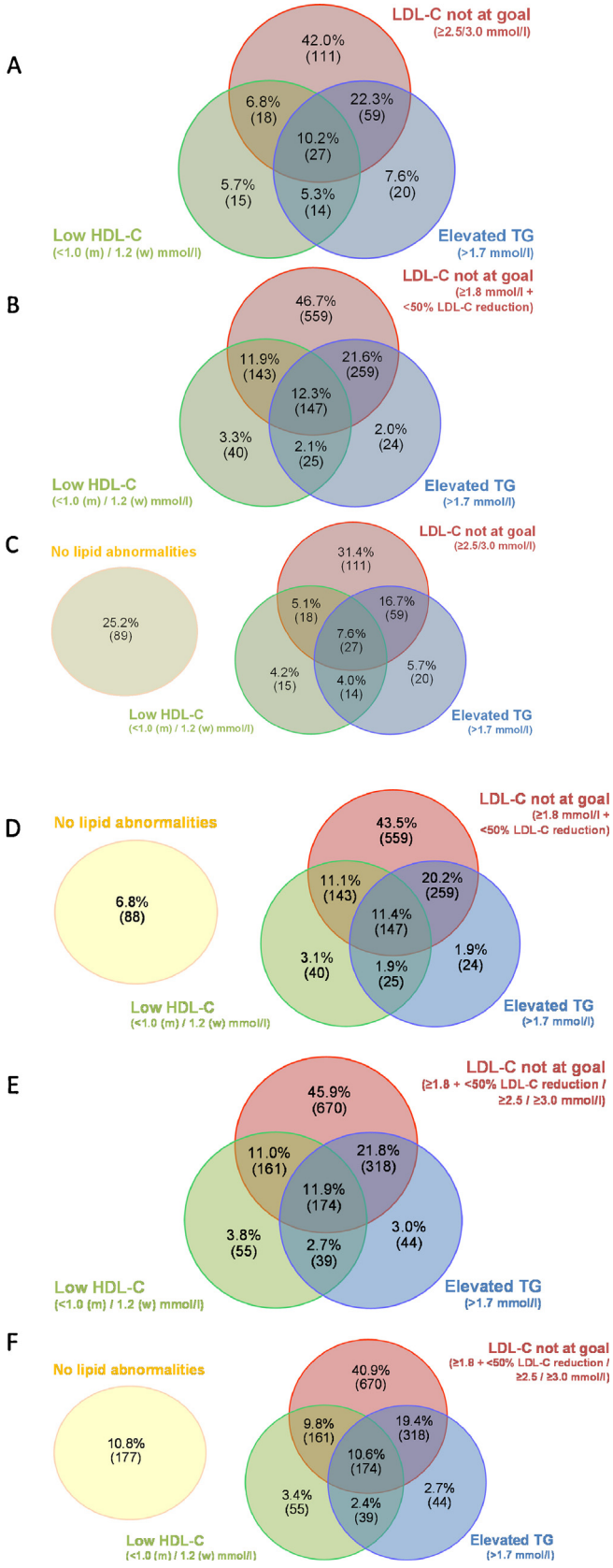

Fig. 3 – Distribution of single and multiple combined lipid abnormalities. (A) Patients at not very high risk (SCORE < 10%) with at least one lipid abnormality [20,23]; (B) patients at very high risk (CVD, diabetes and/or ESC-SCORE ≥ 10%) with at least one lipid abnormality [20,23]; (C) patients at not very high risk (SCORE < 10%) [20,23]; (D) patients at very high risk (CVD, diabetes and/or ESC-SCORE ≥ 10%) [20,23]; (E) patients with at least one lipid abnormality; (F) patients with total lipid profile.

factors strongly positively independently associated with the presence of having all three of the lipid irregularities (in addition to those under age 70, and men).

4. Discussion

Results from DYSIS in the Baltics have indicated that more than three-quarters of statin-treated patients in Estonia, Latvia, and Lithuania were classified as very high-risk for CV complications according to 2011 ESC guidelines. In spite of chronic statin therapy, goal LDL-C levels were not attained in 80.7% of all patients and 86.5% of very high-risk patients. Moreover, low HDL-C and elevated triglyceride levels were observed in 26% and 35% of all statin-treated patients, respectively. Overall, at least one lipid irregularity was detected in 89.2% of patients, with 10.6% displaying all three of the lipid abnormalities simultaneously.

DYSIS analyses conducted in various countries within the EU have identified regional variability in the proportion of patients with LDL-C levels not at goal (despite LMT), including Greece (63.0%), Portugal (62.9%), Spain (63.1%), Ireland (30.8%), Germany (58.1%), and the Netherlands (33.3%) [17,19,25–28]. Also, 37% of patients in Canada did not meet LDL-C goals [18] and an overall analysis of data from the Canadian and European DYSIS cohorts demonstrated that 48.2% of all patients did not have LDL-C at target levels [16]. While earlier analyses reflected different guidelines which may not have been as stringent with regard to the suggested goals, there is nonetheless, a striking proportion of patients with LDL-C levels not at goal (80.7%) in the Baltics, which is much higher than that observed for Canada and several European countries. The observed differences is somewhat driven by the current LDL guidelines (≥1.8 mmol/L or a decrease in LDL-C levels of <50%), which incorporates change in LDL level, an aspect which was not earlier incorporated into LDL-C goal attainment. Explanations for the high rates of dyslipidemia are certainly multifactorial and specific reasons that may relate doctor-patient relationship, inadequate dosing of drugs, unhealthy lifestyle and a certain proportion of patients with lower education, poorer and older people, as well as those outside social support networks. These are affected by a particularly higher risk with respect to smoking, high body weight, lack of physical activity, dietary belief and poor compliance [29–32]. Furthermore, social inequalities may hamper the access to effective statin lowering drugs in the Baltic nations. The DYSIS was not able to capture all of these aspects, however, and so the reasons remain speculative and should be addressed in future surveys.

These data seem to corroborate the fact that the Baltic nations are some of the most profoundly CVD-affected countries within Europe, comprising three out of the four countries with the highest rates of coronary heart disease-related mortality in the EU (OECD, 2012). Also, our findings are in agreement with other recent studies that have begun to monitor CV risk factors in the Baltic region. A study conducted in Latvia identified a high prevalence of CV risk factors, with 75.2% of individuals having high cholesterol, more than two-thirds being overweight, and 44.8% with hypertension [33]. Additionally, the adult populations of Estonia and Lithuania have been found to exhibit high rates of hypertension [34,35]. A report from Estonia illustrated a diabetes prevalence of 7.9% with a steep increase in the elderly (19.8%) on a population based level [36].

In the Baltics, our analyses identified hypertension and obesity (BMI ≥ 30 kg/m^2) to be strongly positively associated with dyslipidemia, involving the presence all three lipid abnormalities, during statin therapy. It has been estimated that 7.5 million deaths each year, or 13% of all deaths, can be attributed to hypertension. This includes 51% of deaths due to strokes and 45% of deaths due to coronary heart disease [1]. Thus, the high prevalence of hypertension known to exist in the Baltics should be targeted as a principal risk factor for preventative and therapeutic interventions in the region. Our findings also indicate tobacco use, alcohol consumption, and diabetes mellitus as risk factors that should be addressed in order to prevent CVD in Estonia, Latvia, and Lithuania.

In addition, our study highlights the limitations of currently available lipid-lowering therapeutic agents and suggests that treatment strategies need to be carefully monitored and optimized to benefit patients. These ideas are supported not only by findings from the DYSIS series, but also by other recent studies analyzing the efficacy of lipid-lowering therapies [14,15]. In addition, it has been suggested that high dose levels of statins and combination therapies could be used more widely to achieve LDL-C targets in high-risk patients [37,38]. For example, the Austrian Cholesterol screening and Treatment (ACT) II study evaluated the effect of lipid-lowering therapies in high-risk, statin-treated patients with elevated LDL-C levels. The ACTII study used a combination therapy consisting of simvastatin and ezetimibe for most patients (73%). Following 12 months of intensified therapy, 40.3% of patients met their LDL-C goals, with a decline in LDL-C levels from baseline of 31.3% and an increase in HDL-C levels of 11.9% [39].

This DYSIS study had several limitations. As a cross-sectional study, data were only collected from a single time-point, and we did not consider long-term CV risk. Also, patient samples were not analyzed in a central laboratory because lipid measurements were made prior to our study, which could possibly introduce procedural variation. In addition, this study is limited in that it couldn't directly assess changes in LDL-C levels. Also, it is possible that patients' treatment regimens could have changed from the time when the original lipid measurement was obtained. However, these variations reflect real-life clinical situations. Finally, it is possible that we introduced self-selection bias because statin treatment was a pre-requisite for inclusion. However, in spite of these potential limitations, the data obtained during this cross-sectional, observational study of the Baltic region has contributed to our knowledge of CV risk, and can promote the advancement of programs and policies aimed at effectively preventing and treating CVD.

5. Conclusions

DYSIS in the Baltics revealed that many statin-treated patients in Estonia, Latvia, and Lithuania did not meet target lipid levels and had a very high risk of CVD. Combating other well-known

CVD risk factors such as obesity and hypertension is vital to reduce the exceptionally high risk for CVD mortality seen in the Baltic nations. In general, our findings support the notion that advancement in dyslipidemia treatment strategies and continued development of programs aimed at lifestyle modification are vital for effectively controlling CV risk.

Funding

This study was funded by Merck & Co Ltd (New Jersey, United States).

Duality of interests

Margus Viigimaa (M.V.), Andrejs Erglis (A.E.), Gustavs Latkovskis (G.L.), Ene Mäeots (E.M.), Žaneta Petrulionienė (Z.P.), Rimvydas Šlapikas (R.S.), and Peter Bramlage (P.Bra.) have received consultancy fees or research funds from Merck & Co Ltd. Anete Gocentiene (A.G.) and Philippe Brudi (P.Bru.) are employees of the sponsor.

Contribution statement

M.V., A.E., G.L., E.M., Z.P., R.S., A.G., and P.Bru. contributed to study concept and design. M.V., A.E., G.L., E.M., Z.P., and R.S. acquired the data and A.G., P.Bru., and P.Bra. interpreted the study data. P.Bra. drafted the manuscript and all other authors revised the article for important intellectual content. All authors read and approved the final manuscript to be published.

Acknowledgments

The authors would like to thank Dr. Claus Jünger and Dr. Steffen Schneider, Stiftung Institut für Herzinfarktforschung, Ludwigshafen, Germany for performing the statistical analyses and to Dr. Myrga Zankel (MSD International) for general support of the study, and Dr. Lori D. Bash (Merck & Co., Inc.) for critical content review. They are indebted to all investigators and patients in the Baltic nations (Estonia, Latvia, and Lithuania) who participated in DYSIS.

REFERENCES

[1] The World Health Organization. Cardiovascular diseases (CVDs). Fact sheet No. 317; 2012.
[2] The World Health Organization in collaboration with the World Heart Federation and the World Stroke Organization. Global atlas on cardiovascular disease prevention and control-policies, strategies and interventions; 2011.
[3] Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren WM, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012): the Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Atherosclerosis 2012;223:1–68.
[4] Kotseva K, Wood D, De Backer G, De Bacquer D, Pyörälä K, Keil U, EUROASPIRE Study Group. EUROASPIRE III: a survey on the lifestyle, risk factors and use of cardioprotective drug therapies in coronary patients from 22 European countries. Eur J Cardiovasc Prev Rehabil 2009;16:121–37.
[5] The World Health Organization. NCD country profiles; 2011, Estonia.
[6] The World Health Organization. NCD country profiles; 2011, Latvia.
[7] The World Health Organization. NCD country profiles; 2011, Lithuania.
[8] Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;366:1267–78.
[9] Deedwania P, Barter P, Carmena R, Fruchart JC, Grundy SM, Haffner S, et al. Reduction of low-density lipoprotein cholesterol in patients with coronary heart disease and metabolic syndrome: analysis of the Treating to New Targets study. Lancet 2006;368:919–28.
[10] Kearney PM, Blackwell L, Collins R, Keech A, Simes J, Peto R, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet 2008;371:117–25.
[11] Cziraky MJ, Watson KE, Talbert RL. Targeting low HDL-cholesterol to decrease residual cardiovascular risk in the managed care setting. J Manag Care Pharm 2008;14:S3–28. quiz S30-21.
[12] Nesto RW. Beyond low-density lipoprotein: addressing the atherogenic lipid triad in type 2 diabetes mellitus and the metabolic syndrome. Am J Cardiovasc Drugs 2005;5:379–87.
[13] Leiter LA, Lundman P, da Silva PM, Drexel H, Junger C, Gitt AK, DYSIS investigators. Persistent lipid abnormalities in statin-treated patients with diabetes mellitus in Europe and Canada: results of the Dyslipidaemia International Study. Diabet Med 2011;28:1343–51.
[14] Kotseva K, Stagmo M, De Bacquer D, De Backer G, Wood D, EUROASPIRE II Study Group. Treatment potential for cholesterol management in patients with coronary heart disease in 15 European countries: findings from the EUROASPIRE II survey. Atherosclerosis 2008;197:710–7.
[15] Sudano I, Hess L, Noll G, Arnet D. Persistent dyslipidemia in statin-treated patients: the focus on comprehensive lipid management survey in Swiss patients. Swiss Med Wkly 2011;141:w13200.
[16] Gitt AK, Drexel H, Feely J, Ferrières J, Gonzalez-Juanatey JR, Thomsen KK, et al. Persistent lipid abnormalities in statin-treated patients and predictors of LDL-cholesterol goal achievement in clinical practice in Europe and Canada. Eur J Prev Cardiol 2012;19:221–30.
[17] Gitt AK, Junger C, Smolka W, Bestehorn K. Prevalence and overlap of different lipid abnormalities in statin-treated patients at high cardiovascular risk in clinical practice in Germany. Clin Res Cardiol 2010;99:723–33.
[18] Goodman SG, Langer A, Bastien NR, McPherson R, Francis GA, Genest JJ, et al. Prevalence of dyslipidemia in statin-treated patients in Canada: results of the DYSlipidemia International Study (DYSIS). Can J Cardiol 2010;26:e330–5.
[19] Horgan S, Crowley J, Feely J, McAdam B, Shanahan E, Vaughan C. Prevalence of dyslipidaemia in statin-treated patients in Ireland: Irish results of the DYSlipidaemia International Study (DYSIS). Ir J Med Sci 2011;180:343–9.
[20] Catapano AL, Reiner Z, De Backer G, Graham I, Taskinen MR, Wiklund O, et al. ESC/EAS Guidelines for the

management of dyslipidaemias The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Atherosclerosis 2011;217:3–46.
[21] Grundy SM, Cleeman JI, Merz CN, Brewer Jr HB, Clark LT, Hunninghake DB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004;110:227–39.
[22] Roberts WC. The rule of 5 and the rule of 7 in lipid-lowering by statin drugs. Am J Cardiol 1997;80:106–7.
[23] Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren WM, et al. European guidelines on cardiovascular disease prevention in clinical practice (version 2012): the fifth joint task force of the European society of cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). Int J Behav Med 2012;19:403–88.
[24] Parzen E. On estimation of a probability density function and mode. Ann Math Stat 1962;33:1065–76.
[25] da Silva PM, Cardoso SM. Persistent lipid abnormalities in patients treated with statins: Portuguese results of the Dyslipidemia International Study (DYSIS). Rev Esp Cardiol 2011;30:47–63.
[26] Gonzalez-Juanatey JR, Millan J, Alegria E, Guijarro C, Lozano JV, Vitale GC. Prevalence and characteristics of lipid abnormalities in patients treated with statins in primary and secondary prevention in Spain. DYSIS-Spain Study. Rev Esp Cardiol 2011;64:286–94.
[27] Liberopoulos E, Vlasserou F, Mitrogianni Z, Papageorgantas I, Elisaf M, DYSIS-GREECE Investigators. Prevalence and risk distribution of residual dyslipidemia in statin-treated patients in Greece. Angiology 2012;63:184–93.
[28] Strang AC, Kaasjager HA, Basart DC, Stroes ES. Prevalence of dyslipidaemia in patients treated with lipid-modifying drugs in the Netherlands. Part of the dyslipidaemia international survey. Neth J Med 2010;68:168–74.
[29] Pomerleau J, McKee M, Robertson A, Kadziauskiene K, Abaravicius A, Bartkeviciute R, et al. Dietary beliefs in the Baltic republics. Public Health Nutr 2001;4:217–25.
[30] Pomerleau J, McKee M, Robertson A, Vaasc S, Kadziauskiene K, Abaravicius A, et al. Physical inactivity in the Baltic countries. Prev Med 2000;31:665–72.
[31] Pomerleau J, Pudule I, Grinberga D, Kadziauskiene K, Abaravicius A, Bartkeviciute R, et al. Patterns of body weight in the Baltic Republics. Public Health Nutr 2000;3: 3–10.
[32] Pudule I, Grinberga D, Kadziauskiene K, Abaravicius A, Vaask S, Robertson A, et al. Patterns of smoking in the Baltic Republics. J Epidemiol Community Health 1999;53:277–82.
[33] Ērglis A, Dzērve V, Pahomova-Strautiņa J, Narbute I, Jēgere S, Mintāle I, et al. A population-based cross-sectional study of cardiovascular risk factor in Latvia. Medicina (Kaunas) 2012;48:310–6.
[34] Org E, Veldre G, Viigimaa M, Juhanson P, Putku M, Rosenberg M, et al. HYPEST study: profile of hypertensive patients in Estonia. BMC Cardiovasc Disord 2011;11:55.
[35] Reklaitiene R, Tamosiunas A, Virviciute D, Baceviciene M, Luksiene D. Trends in prevalence, awareness, treatment, and control of hypertension, and the risk of mortality among middle-aged Lithuanian urban population in 1983–2009. BMC Cardiovasc Disord 2012;12:68.
[36] Eglit T, Rajasalu T, Lember M. Prevalence of diabetes and impaired glucose regulation in Estonia. Diabet Med 2011;28:504–5.
[37] Bandgar TR, Faruqui AA. Managing dyslipidaemia: evolving role of combination therapy. J Indian Med Assoc 2011;109:549–52.
[38] Ito MK. Dyslipidemia: management using optimal lipid-lowering therapy. Ann Pharmacother 2012;46:1368–81.
[39] Eber B, Lautsch D, Fauer C, Drexel H, Pfeiffer KP, Traindl O, et al. Can LDL-cholesterol targets be achieved in a population at high risk? Results of the non-interventional study ACT II. Curr Med Res Opin 2012;28:1447–54.