An attempt to make lipid-lowering therapy more effective in Hungary. The results of MULTI GAP 2010 and the PLUS Program

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Abstract

Introduction: The primary goal of lipid-lowering therapy is the attainment of low-density lipoprotein cholesterol (LDL-C) target levels.

Material and methods: The MULTI GAP (MULTI Goal Attainment Problem) 2010 is a part of surveys started a few years ago, in which the lipid results of 1540 patients treated by general practitioners (GPs) and specialists were measured. The data were compared to the results of similar studies involving 15,580 patients between 2004 and 2009.

Results: In 2010 the mean LDL-C level (± SD) of patients treated by GPs was found to be 3.01 ±1.0 mmol/l. The target of 2.50 mmol/l was achieved by 32%, with a mean LDL-C level of 2.84 ±1.0 mmol/l and an achievement rate of 39% in patients treated by specialists. The results of comparisons starting from 2004 showed a marked improvement every year in the beginning, but in the last 3 years stagnation was observed. In 2010 in addition to the MULTI GAP main study, a group of physicians took part in special training called the Plus Program. As a result of this, the LDL-C level was 0.18 mmol/l lower in 114 of the GPs' patients ($p = 0.088$) and 0.27 mmol/l ($p < 0.0001$) lower in 313 of the specialists' patients, with a significantly better, 42% ($p = 0.045$) and 50% ($p = 0.001$), goal attainment rate, respectively.

Conclusions: The 2010 MULTI GAP study shows that the quality of lipid-lowering therapy in Hungary seems to be in stagnation. The results of the PLUS Program suggest that continuous training of doctors is the key to further improvement.

Key words: prevention, risk factors, hypercholesterolaemia, LDL cholesterol.

Introduction

Despite the clear improvement in recent years, cardiovascular disease (CVD) continues to be the leading cause of death in mortality statistics [1]. Coronary heart disease (CHD) is a global epidemic and its prevention is one of the biggest challenges in contemporary medicine. The European Heart Health Charter highlights that beside the increasing funding spent

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for the treatment of CVD in developed countries, a stronger emphasis should be placed on prevention [2, 3]. The recommendations and the cardiovascular prevention in daily practice should be bridged as soon as possible [4].

It is a well-known fact that the main reasons leading to the development of CHD are related to lifestyle. This is supported by the INTERHEART study carried out in 52 countries which proved that several well-defined and reversible risk factors are responsible for 90% of heart attacks [5]. One of the most important risk factors is hyperlipidaemia. Lipid-lowering therapy has outstanding importance in the treatment of high-risk patients. What is the situation of lipid-lowering therapy in Hungary and how could the quality of treatment be improved further? Based on the results of surveys carried out systematically since 2004 by general practitioners (GPs) and specialists among high-risk patients, the frequencies of target level attainment and alterations of lipid-lowering treatments are comparable. Besides presenting these results and those of MULTI GAP (MULTI Goal Attainment Problem) 2010, the recent data are compared to those observed in patients of a group of physicians who received special training.

Material and methods

The trends in lipid-lowering treatment were studied using surveys (CEL Program 2004 and 2005, KONSZENZUS-CEL Program 2006, REALITY 2004 and 2007 studies, MULTI GAP 2008 and 2009) performed on high cardiovascular risk patients of GPs and specialists in Hungary. From the period between 2004 and 2008, the data of 12 317 [6], and from MULTI GAP 2009 those of 3563 patients [7] were processed.

In the MULTI-GAP 2010 study we analysed data and treatment strategies of 1540 patients from 136 specialists and 47 GPs (10-15 patients per physician were enrolled) using a structured questionnaire. The previous publication on 2010 data [8] did not separate the patients of the main study from those of the Plus Program, and in this study we used only the data of the patients being conformed with the former publications. The patients gave their consent to participate; the study was conducted in accordance with the Declaration of Helsinki and ICH-GCP (International Conference on Harmonisation – Good Clinical Practice).

Out of physicians participating in MULTI GAP 2010, 26 specialists and 9 GPs also took part in the PLUS Program with 397 and 117 patients, respectively. In this framework, these colleagues received special education related to lipid treatment, attended lectures on the guidelines of the Hungarian consensus conference [9], and received written material related to this topic as well. They were supplied with a calculator to determine the low-density lipoprotein cholesterol (LDL-C) level and also with software to analyse target level achievements which showed the proportion of treated patients attaining the target level in their whole practice, thus helping therapy and drawing attention to the insufficiencies of lipid-lowering therapy.

The whole MULTI GAP patient group (including the Plus Program patients) included 197 cases of unstable angina, 590 cases of previous myocardial infarction, 275 cases of vascular operation due to peripheral arterial disease, 432 cases of stroke and 275 of transient ischaemic attack, 924 diabetic patients and 1770 with hypertension. The existence and extent of smoking, as well as the sex, age, body mass index (BMI) and waist circumference were recorded. 842 women and 1125 men participated in the study; their mean age was 64.4 ±10 years. The doctors also estimated patient compliance based on frequency of statin prescription, the patients' knowledge and questioning the patients.

The risk classification of patients was performed according to the 4th Hungarian Cardiovascular Consensus Conference recommendations [9]. All patients belonged to the high cardiovascular risk category, and because they also had a history of vascular events and/or were diabetic, they had LDL-C targets of ≤ 2.50 mmol/l.

Statistical analysis

For categorical variables we used frequencies of valid cases. For continuous variables means and medians are presented. Significance tests were performed by χ^2 test for categorical and by ANOVA for continuous variables (with Fisher's least significant difference test method for multiple comparisons). Asymmetric 2-sided scores were considered. Values of p (two-tailed) below 0.05 were accepted as significant. All statistical analyses were performed by SPSS.

Results

The MULTI GAP 2010 main study involved 1540 patients. The GPs' patients had a mean LDL-C level (± SD) of 3.01 ±1.0 mmol/l, while those of the specialists had 2.84 ±1.0 mmol/l. Figure 1 demonstrates changes of LDL-C level between 2004 and 2010, showing a decrease of 0.77 mmol/l for patients treated by GPs whereas in patients treated by specialists a decrease of 0.50 mmol/l could be observed during this 7-year period. In 2010, 32% of the GPs' patients achieved the 2.50 mmol/l LDL-C target value, while for patients treated by specialists the corresponding proportion was 39%; Figures 2 and 3 show changes in rates of patients achieving the target levels. In addition to the MULTI
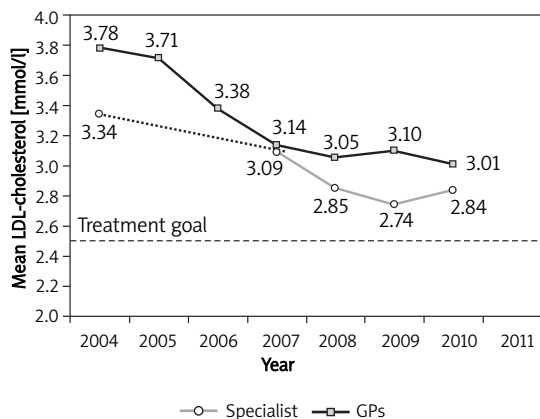
Figure 1. Change in mean LDL-cholesterol levels of high cardiovascular risk patients treated by GPs and specialists, over the years
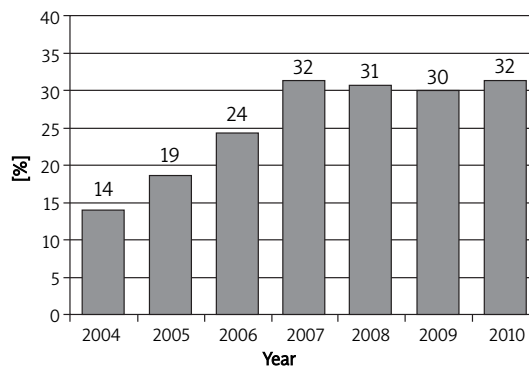

Figure 2. Changes in the ratio of patients reaching the target 2.5 mmol/l of LDL-cholesterol level treated by GP's over the last years
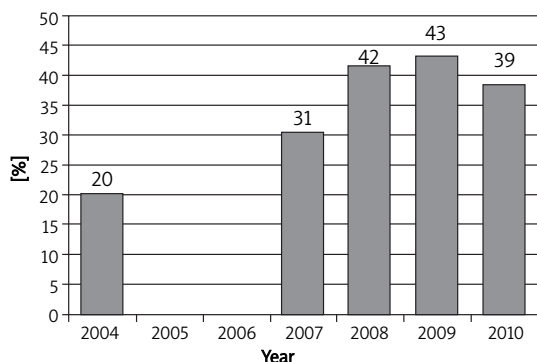

Figure 3. Changes in the ratio of patients reaching the target 2.5 mmol/l of LDL-cholesterol level treated by specialists over the last years

GAP main study, a group of doctors underwent special training in 2010, called the Plus Program. Table I shows the mean LDL-C level of the 427 patients treated by GPs and specialists and the percentage of them achieving the level of 2.50 mmol/l. The GP patients experienced a reduction of 0.18 mmol/l in their mean LDL-C level, while those of specialists had a decrease of 0.27 mmol/l. Accordingly, a significant (10% and 11%) increase occurred in the 2.50 mmol/l LDL-C attainment rate in both GPs' and specialists' patients (increasing to 42% and 50%, respectively). Table II presents the

mean body mass index values and the occurrence of hypertension, smoking and diabetes in the MULTI GAP 2010 basic study and the PLUS Program in the patient groups treated by GPs and specialists. Also shown are the values of significance between the MULTI GAP 2010 study and the Plus Program and between the GPs' and specialists' patients.

In our study we separated male and female groups when analysing the mean LDL-C levels. These, along with the mean BMI values, and the occurrence of hypertension, smoking and diabetes in the two genders are presented in Table III. The LDL-C in women was 6.2% (0.17 mmol/l) higher than the value considering all patients, and similar rates were found among male and female patients of physicians participating and not participating in the Plus Program (0.15 mmol/l and 0.18 mmol/l difference, respectively). The 2010 MULTI GAP study also evaluated the physicians' lipid-lowering medical treatment compliance. This was based on questioning the patient and the frequency of drug prescriptions, and the result was given in percentage. Four groups were formed based on compliance: 70% or below, 71-80%, 81-90% and over 90% of patients were considered cooperative in each group, respectively. The 2.50 mmol/l LDL-C target achievement rate was 24%, 31%, 39% and 41%, respectively (Figure 4).

We examined what doses of statin were applied in the patients reaching or not reaching the target.

Table I. The mean LDL cholesterol and the achievement rate of 2.50 mmol/l target LDL cholesterol in the MULTI GAP 2010 basic study and PLUS Program

	GPs			Specialists		
	Patient number	LDL cholesterol level [mmol/l]	Target achieve-ment [%]	Patient number	LDL cholesterol level [mmol/l]	Target achieve-ment [%]
MULTI GAP 2010	397	3.01 ±1.00	32	1143	2.84 ±0.99	39
PLUS Program	114	2.83 ±0.95	42	313	2.57 ±0.90	50
	p = 0.088		*p* = 0.045	*p* < 0.0001		*p* = 0.001

Table II. The mean body mass index values and the occurrence of hypertension, smoking and diabetes in the MULTI GAP 2010 basic study and PLUS Program in the patient groups treated by GPs and specialists

	GPs	Specialists	Value of p
Body mass index [kg/m²]			
MULTI GAP 2010	28.8 ±4.9	29.2 ±5.0	0.152
PLUS Program	28.9 ±5.4	29.4 ±4.8	0.399
	p = 0.763	p = 0.537	
Hypertension [%]			
MULTI GAP 2010	93	89	0.038
PLUS Program	82	94	< 0.001
	p = 0.001	p = 0.011	
Smoking [%]			
MULTI GAP 2010	28	28	0.782
PLUS Program	37	31	0.228
	p = 0.060	p = 0.439	
Diabetes mellitus [%]			
MULTI GAP 2010	39	52	< 0.001
PLUS Program	30	43	0.011
	p = 0.089	p = 0.009	

Table III. The distribution of LDL cholesterol level, body mass index and the occurrence of hypertension, smoking and diabetes according to gender

	Men	Women	Value of p
LDL cholesterol level [mmol/l, mean ± SD]			
Total	2.76 ±0.95	2.93 ±1.02	0.001
MULTI GAP 2010	2.81 ±0.96	2.99 ±1.03	0.001
PLUS Program	2.58 ±0.89	2.73 ±0.96	0.091
Body mass index [kg/m², mean ± SD]			
Total	29.2 ±4.8	28.9 ±5.2	0.227
MULTI GAP 2010	29.2 ±4.8	28.9 ±5.2	0.233
PLUS Program	29.3 ±4.6	29.1 ±5.6	0.753
Hypertension [%]			
Total	90	91	0.372
MULTI GAP 2010	90	91	0.517
PLUS Program	90	92	0.482
Smoking [%]			
Total	36	20	< 0.001
MULTI GAP 2010	35	20	< 0.001
PLUS Program	40	21	< 0.001
Diabetes mellitus [%]			
Total	48	44	0.056
MULTI GAP 2010	49	47	0.405
PLUS Program	45	32	0.009

To compare the efficacy of different statins we calculated simvastatin equivalent doses [10, 11]. Those who did not reach the 2.50 mmol/l target level had a daily simvastatin dose of 39.4 mg, while those who achieved the target were on 42.2 mg (non-significant difference, p = 0.11). During the treatment the doctors also applied ezetimibe as combination therapy in order to achieve the target in addition to statins. The rate of administration of combination therapy was 10% in the MULTI GAP main study and 22% in the PLUS Program (p 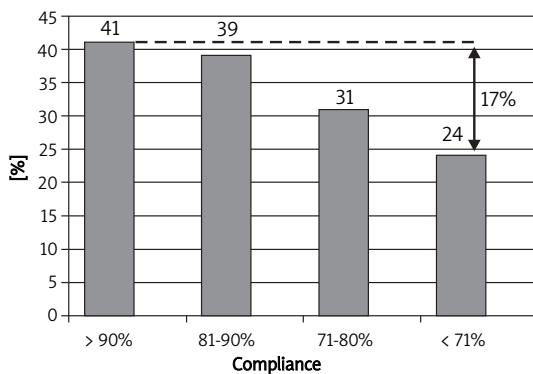< 0.001). The application of combination therapy significantly helped to achieve the 2.50 mmol/l LDL-C target in both MULTI GAP 2010 and the PLUS Program (p < 0.001) (Figure 5).

Discussion

The results of the INTERHEART study showed that in 90% of cases, well-defined risk factors are responsible for the development of myocardial
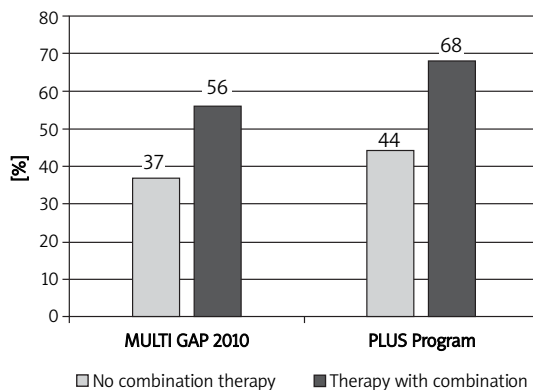

Figure 4. The relationship between the attainment of 2.5 mmol LDL-cholesterol level and the patients compliance in the MULTI GAP study

Figure 5. The attainment rate of 2.5 mmol/l LDL-cholesterol target level in MULTI GAP 2010 study and PLUS Program according to the application of combination therapy

infarction [5]. These results give a kind of encouragement to those who are engaged in prevention and to health policy, since they show that CVD is preventable and that a greater role should be given to achieving changes in lifestyle.

The STENO-2 study compares the importance of treatment of 3 major risk factors (hyperlipidaemia, hypertension and diabetes mellitus) in the development of cardiovascular events in type 2 diabetic patients. The 13.3-year follow-up of 80 patients receiving intensive therapy and 80 receiving standard therapy confirmed the primacy of intensive risk factor treatment and of a multifactorial approach [12, 13]. In the study there was a significant difference in attaining target values of the different risk factors. The best ratio was that of cholesterol, followed by hypertension and HbA_{1c}.

The analysis of Yudkin *et al.*, based on results of various intervention and epidemiological studies, compares the number of patients needed to treat for the prevention of one event (NNT = number needed to treat) with the same risk factors. With 1 mmol/l cholesterol reduction 59.5 patients, with 10/5 mmHg blood pressure reduction 61.8, and with 0.9% reduction in HbA_{1c} 140.3 patients have to be treated for 5 years to prevent one fatal or non-fatal heart attack or sudden cardiac death [14]. The STENO-2 study and Yudkin's meta-analysis demonstrate that the incidence of cardiovascular events can be influenced the best by reducing the cholesterol level; this is the activity in which the target levels would be the easiest to attain.

The key element in the prevention guidelines is the adequate reduction of lipids in stable and unstable ischaemic conditions [15]. The last 1.5-2 decades have resulted in the appreciation of lipid-lowering therapy in the developed countries and this, with some delay, arrived in Hungary as well. The EUROASPIRE studies also showed that in patients suffering from CHD the treatment of all risk factors improved, but the changes in lipid goal achievements were extremely good [16, 17].

The extent of the lipid-lowering therapy is determined by the goal values depending on the risk categories. In its spreading in Hungary the consensus conference held every 2 years has had notable achievements which help to keep the topic of prevention before the public eye. Moreover, the results of conferences are constant subjects of continuous medical education, and publications about the consensus are constant themes in the medical journals. Currently the recommendations of the 4th Hungarian Cardiovascular Consensus Conference are considered as standards in cardiovascular prevention [9].

The publication of outstanding results of the clinical studies performed with statins also contributes to applying more frequently the representatives of this class of drugs in Hungary as well. Data of systematic surveys of recent years show that the LDL-C attainment rate in patients with high cardiovascular risk is continuously increasing. The increased activity of pharmaceutical companies also played an important role in this, on one hand by promoting and propagating the principles of prevention and the results of consensus conferences, and on the other hand by presenting lipid-lowering drugs, including generic statins, at low prices to the colleagues. It has been proved that lipid-level reduction plays a considerable role in the improvement of cardiovascular mortality in Hungary [18] but due to the absence of accurate data its extent cannot be given. The increasing use of combination therapy also contributes to these positive results. In the MULTI GAP 2010 study the application rate of combination treatment was 10%. However, it should be noted that in patients of doctors properly educated by the PLUS Program the administration of combination therapy was more frequent (22%), which resulted in a significantly greater LDL-C target attainment (Figure 5).

Results of MULTI GAP 2010 taking into account also the trends of previous years show that the upward trend has been broken; the significant improvement observed initially each year is now hardly noticeable. Li *et al.* in the population-wide representative National Health and Nutrition Examination Survey conducted in the U.S. with a large number of individuals between 1999 and 2006 found a decrease of the LDL-C levels in men from 3.25 ±0.03 to 3.02 ±0.02, and that in women from 3.11 ±0.03 to 2.98 ±0.03 mmol/l ($p < 0.001$) [19]. In Hungary, the observed decrease during the same period (0.77 mmol/l for GPs, 0.50 mmol/l for specialists) was significantly higher, but it should not be forgotten that the latter record came from high-risk patients treated by lipid-lowering drugs, and yet it is noteworthy that the U.S. average LDL-C level is essentially similar to that of high-risk, treated patients of Hungary. Farzadfar *et al.*, analysing global trends, found (not in high cardiovascular risk patients) in higher-income countries (Western Europe, North America and Australia) a 0.2 mmol/l decrease, and in Eastern and Central Europe a 0.2 mmol/l decrease in LDL-C level during a decade [20].

A favourable change in the frequency of risk factors causes a significant reduction in cardiovascular mortality [21]. According to the results of the LTAP study, the achievement rate of LDL-C target levels rose in 9 countries on average from 18% to 67% in 10 years [22]. The Hungarian trends are improving as well, but the results are less favourable in international comparative terms [15, 23, 24].

In 2010, besides MULTI GAP, the standard quality measurement of lipid-lowering therapy, a new trial was carried out in which a smaller group of doctors received a special education named the Plus Program. The results proved that education of GPs and specialists can boost further improvement of reaching the target level, i.e. a better knowledge of principles and practices of prevention, and application of the lipid-lowering computer program results in the improvement of treatment. The importance of education is also emphasized in the publication of Katsiki *et al.* [25].

It is well known that women have less favourable indicators of cardiovascular prevention [26]. Lipid lowering and achieving the targets in Hungary seem to be no exception. Women's LDL-C level was higher by 6.2%, 0.17 mmol/l. The trend was similar among male and female patients of the PLUS Program (0.15 mmol/l is not a statistically significant difference due to the small sample size), which means that a better understanding of the principles of prevention itself does not lead to more favourable rates. Perhaps the indicators would improve if the training drew more attention to careful treatment of women.

The administration of ezetimibe results in a lower LDL cholesterol level [27]. Our results demonstrate that the frequent use of combination therapy helps to achieve the target levels (Figure 5). In patients reaching the target values, higher statin doses were applied (undoubtedly, the difference was not statistically significant).

The effectiveness of drug therapy largely depends on the therapeutic cooperation of the patients [28]. The meta-analysis of Simpson *et al.* found a correlation between therapeutic adherence and the occurrence of clinical events, including deaths [29]. Rasmussen *et al.* studied the relationship of long-term survival and evidence-based pharmacotherapy in post-infarction patients. More than 31 thousand patients were followed and it was concluded that good adherence to statins also led to a reduction in mortality [30]. In our study, we found a linear correlation between the patients' cooperation in compliance of drug taking and achievement of the LDL-C target value (Figure 4). Between the good and bad compliance group there was a 17% difference in the target level attainment rate, which in the long term would evidently cause a difference in the occurrence of clinical events.

Overall, the 2010 MULTI GAP study showed that the improvement of quality of lipid-lowering therapy in Hungary came to a stop. The results of the PLUS Program suggest that the continuous training of doctors is the key to further improvement. This training must draw attention to women's increased risk and the need for their more careful treatment. Achievement of target values is favourably influenced by improved patient compliance. Each consultation between doctor and patient should draw the patient's attention to the fact that the effectiveness of lipid-lowering therapy will deliver the expected anti-atherosclerotic results and lowering effect on cardiovascular events only if medication compliance is appropriate. Stricter follow-up of patients also improves the therapeutic collaboration. Every lipid-level control should include a revision of the therapy. Our study also confirmed that by applying higher doses of statins together with combination treatment a greater lipid-lowering effect and better target level attainment could be achieved.

Acknowledgments

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Laszlo Mark, György Paragh, Istvan Karadi, Istvan Reiber, Gyula Pados, Zoltan Kiss

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