

The Effect of Switching to the High-Efficient Rosuvastatin on the Success of Lipid Lowering Therapy in High Risk Patients. The CORVUS (Controlled Targets for High Vascular Risk Patients Using Effective Statins) Study

Laszlo Mark^{1*}, Istvan Reiber², Laszlo Bajnok³, Istvan Karadi⁴ and György Paragh⁵

¹Pandy Kalman Bekes County Hospital, 2nd Department of Medicine – Cardiology, Gyula, Hungary

²St. George Fejer County Hospital, 4th Department of Medicine, Szekesfehervar, Hungary

³1st Departments of Medicine, University of Pecs, Pecs, Hungary

⁴3rd Departments of Medicine, Semmelweis University, Budapest, Hungary

⁵Medical and Health Science Centre, University of Debrecen, 1st Department of Medicine, Debrecen, Hungary

Abstract

Aim: Achievement of target lipid levels is a one of the most important part of the cardiovascular risk reduction to which an obvious way is to switch from current drug to a stronger statin.

Method: In a 3-month, multicenter, prospective, observational, non-interventional open-label study the change of lipid levels and the rate of target level attainment were investigated in 1385 high cardiovascular risk patients, administering, if possible, rosuvastatin in those with lipid levels over the target values.

Results: During the 3-month treatment period the level of total cholesterol decreased by 25.2%, LDL-cholesterol by 35.0%, triglyceride by 21.0% and HDL-cholesterol level increased by 5.1%. At the end of the study 96% of the patients were treated with rosuvastatin in monotherapy or in combination. At the third month the rate of achieving LDL-cholesterol target level was 57.7% and that of HDL-cholesterol target level was 66.7% and in case of triglyceride level 48.2%. The majority of patients (1077 persons) belonged to the very high risk category according to the guidelines of 3rd Hungarian Cardiovascular Consensus Conference. Among them the achievement rate of an LDL-cholesterol level of 1.8mmol/L was proved to be 19.0%.

Conclusion: The study confirmed that more frequent use of a high-efficient statin (rosuvastatin) by specialists has a beneficial effect on lipid parameters and also facilitates a higher rate of achieving target lipid levels, but to be more efficient, mainly in the very high risk category cases, the combination therapy has to be used more often.

Keywords: Atherosclerosis; Prevention; Cholesterol; Triglyceride; HDL-cholesterol; Statin

Introduction

Despite the gradual improvement experienced over the last decades atherosclerotic heart disease remained the leading cause of death in Europe and North-America. Hungarian morbidity and mortality data are unfavorable even if compared to most of neighboring East-Central European countries [1]. At the same time a favorable change occurred also in Hungary regarding the mortality data after 1993, as a result of this life expectancy at birth increased by 4.14 years between 1993 & 2006 to which improvement of cardiovascular mortality contributed by 1.85 years [2].

In the development of ischemic heart disease beside hypertension, smoking and diabetes mellitus [3,4] abnormal lipid levels play a predominant role. Reduction of high cholesterol level is emphasized by treatment guidelines which also support the importance of achieving the prescribed levels, i.e. target values. Surveys on lipid lowering practice of recent years demonstrate that total and LDL cholesterol levels are achieved more and more frequently [5-8], however, despite the considerable and promising improvement a large gap remains between daily practice and the possibilities [9-11]. According to Hungarian studies the most common reason for failure of target level achievement is that the physicians do not modify the therapy when the patient comes with the laboratory results showing inappropriate lipid levels [10,12].

Out of lipid lowering therapies statins are the first choice drug. Numerous randomized clinical endpoint studies demonstrated their

favorable effects on the improvement of morbidity and mortality. There is a significant difference in the lipid lowering effect of each statins, therefore it does matter which statin in what dose is applied. Our objective was to investigate the quality of lipid lowering therapy among controlled conditions in high and very high cardiovascular risk patients and to assess the effect of high efficient statin (rosuvastatin) on target lipid level achievement.

Patients and Methods

The CORVUS (Controlled Targets for High Vascular Risk Patients Using Effective Statins) study was a 3-month, multicenter, prospective, observational, non-interventional open-label clinical study carried out in 26 sites of Hungary between May and December 2009, and involving 1385 patients.

***Corresponding author:** L. Mark, MD, PhD, 2nd Department of Internal Medicine-Cardiology, Pandy Kalman Bekes County Hospital, Semmelweis u. 1, P.O. Box 46, 5701 Gyula, Hungary, Tel: +36-209288053; Fax: +36-66526543; E-mail: mark@pandy.hu

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The primary outcome measures were percent rate of patients achieving target LDL cholesterol goals and the percent rate of patients achieving 50% or more reduction in LDL-cholesterol. The secondary outcome measure was percent rate of patients achieving target secondary (total cholesterol, triglyceride, HDL-cholesterol) goals.

Patients at high or very high cardiovascular risk, aged over 18 years, receiving already statin therapy or requiring lipid lowering therapy, with a cholesterol (total cholesterol and/or LDL cholesterol) level above target value were eligible for the data collection program.

1385 patients spent an average of 99.1 days (SD ± 21.6 days) in the study. Table 1 summarizes the co-morbidities of the participants, and (Table 2) shows lipid lowering drugs taken at baseline (note: more than one medicine may belong to one patient). Based on co-morbidities the patients belonged to such a high risk category that according to the guidelines of 3rd Hungarian Cardiovascular Consensus Conference (HCCC) the target LDL cholesterol level was at least 2.5 mmol/L. HDL cholesterol target value in male was 1.0, in female 1.3 mmol/L, and that of triglyceride was 1.7 mmol/L [13].

1077 out of 1385 participants (78%) was found to be at very high risk according to HCCC guidelines, 538 male and 539 female patients. Their mean age was 62.8±10.0 years, 1071 of them came back for visit 2 and 1060 for visit 3.

The survey was approved by the Hungarian Medical Research Council and participants gave informed consent. The study was conducted in accordance with the Declaration of Helsinki and GCP-ICH (International Conference on Harmonization Good Clinical Practice).

Statistics

Data collection and statistical analyses was performed by WEB2 Research Ltd, Hungary. Statistical analyses were performed with SPSS 7.5. Descriptive statistics are presented as frequencies and percentages for categorical variables and as the mean values ± SD for continuous variables. Categorical variables were compared using the chi² test. Paired Student's t-test was used for continuous parametric variables. In statistical analyses the confidence intervals (CI) were calculated at a significance level of 95%.

Results

Totally 1385 patients, 718 males (51.8%) and 667 females (48.2%) took part in the study, mean age was 63.0 (SD ±10.1 years), minimum and maximum value was 28 and 89 years. Body weight at the first visit was 82.8 ±14.6 kg; body mass index was 29.0±4.4 kg/m² which changed non significantly at visit 3 to 81.8±13.8 kg and 28.63± 4.25 kg/m².

Out of patients participating at visit 1, 1379 came back for visit 2 and 1358 for visit 3. Table 3 summarizes the lipid lowering drugs recommended at the different visits. Administration of rosuvastatin predominates and the recommended dose increased continuously as well; at visit 1 the average was 15.4 mg, at visit 2, 16.6 mg and at visit 3, 17.4 mg. The proportion of maximal dose of 40 mg was not high; however, it increased continuously at each visit (4.8%, 6.8% and 9.1% respectively).

Lipid levels measured at each visit is demonstrated by (Table 4). Between visit 1 and 3 level of total cholesterol decreased by 25.2%, LDL-cholesterol by 35.0%, triglyceride by 21.0%, at the same time the level of HDL cholesterol showed an increase of 5.1%.

	Patient number	%
Hypertension	1314	94.9
Diabetes mellitus	589	42.5
prior MI	485	35.0
CHD	954	68.9

Table 1: Co-morbidities of study participants.

	Patient number (n=1385)	%
Atorvastatin	616	44.5
Simvastatin	421	30.4
Fluvastatin	123	8.9
Inegy	24	1.7
Ezetimibe	20	1.4
Fenofibrate	14	0.1

Table 2: Lipid lowering drugs taken by the patients at the time of entering the study (more than one drug may belong to one patient).

	Visit 1		Visit 2		Visit 3	
	Patient number (n=1385)	%	Patient number (n=1379)	%	Patient number (n=1358)	%
Rosuvastatin	1308	94.4	1326	96.2	1311	96.5
Ezetimibe	64	4.7	72	5.2	99	7.3
Atorvastatin	30	2.2	19	1.4	18	1.3
Simvastatin	21	1.5	15	1.1	16	1.2
Fenofibrate	28	2.0	25	1.8	30	2.2

Table 3: Proportion of recommended lipid lowering drugs at the visits (drugs with an occurrence of at least 1%; more than one drug may belong to one patient).

		Visit 1	Visit 2	Visit 3
Total cholesterol	(mmol/ L±SD)	6.09±1.31	4.83±1.02	4.51±0.88
LDL-cholesterol	(mmol/L±SD)	3.73±1.14	2.73±0.89	2.44±0.75
HDL-cholesterol	(mmol/L±SD)	1.28±0.36	1.31±0.35	1.33±0.32
Triglyceride	(mmol/L±SD)	2.49±2.03	1.96±1.17	1.85±1.23

Table 4: Lipid levels at each visit in the entire population.

Primary endpoint of the study was the rate of achieving target LDL value (in this study population at least 2.5 mmol/L based on the 3rd HCCC guidelines). This rate of 12.7% found at visit 1 increased to 42.9% by the time of visit 2 and 57.7% by visit 3 (Figure 1).

The achievement rate of HDL target levels (1.0 mmol/L in male and 1.3 mmol/L in female patients) was 59.8% at visit 1 and 66.7% at visit 3. Triglyceride target value of 1.7 mmol/L was achieved by 30.1% of patients at baseline, and 48.2% at the end of study (Figure 2).

Striving for total lipid control we examined how many patients managed to reach the LDL-cholesterol level of 2.5 mmol/L and HDL cholesterol and triglyceride target levels altogether at visit 1 and visit 3. These ratios are presented by (Figure 3).

Out of 1385 participating patients 1077 belonged to the very high risk category according to the 3rd HCCC guidelines. Mean lipid values of this patient group are showed by Table 5. Achievement rate of LDL-cholesterol target value of 1.8 mmol/L was in this population 2.7%, 13.9% and 19.0% at visit 1, 2 and 3, respectively. The target value of HDL cholesterol level was reached by 51.8%, 59.0% and 62.1%, that of triglyceride level by 22.5%, 34.1% and 40.2% at visit 1 – 3, respectively.

Imaging procedures of atherosclerotic process proved that regression can be expected only if the patient's LDL level decreases at least below 50% of baseline value [14,15]. In this study the lipid values measured before introducing the lipid lowering drug were not known as patients were already receiving therapy at the time of entering the study (just as it is the case in most patients in the everyday practice). Nevertheless, we had the opportunity to check how many patients managed to reach the 50% decrease at follow-up visits compared to the LDL-cholesterol level measured at baseline. The rate of these patients was 14.5% at visit 2 and 21.1% at visit 3.

The number of all treatment related adverse events was found to be 35, among them pain in the muscles and in the joints predominated in 19 cases (emphasizing that in 7 persons it was only a slight complaint), abdominal complaint was experienced in 7 patients, swollen legs in 1 patient, increase of creatine kinase in 5 and increase of liver enzymes in 3 patients. Lipid lowering therapy had to be stopped in 5 cases; 2 patients had pain in the muscles, 1 had pain in the joints, 1 patient developed abdominal complaints and in 1 patient significant increase of liver enzymes was experienced. Relying upon these findings the occurrence of side effects leading to therapy discontinuation was found to be below 4 per thousand.

Discussion

A part of target value achievement studies is comparative clinical study in which the results of administration of drugs applied according to a predefined protocol are assessed. Another part of studies strives to determine the directions of medical practice. Surveys which suggest a better practical use of treatment principles to the colleagues belong

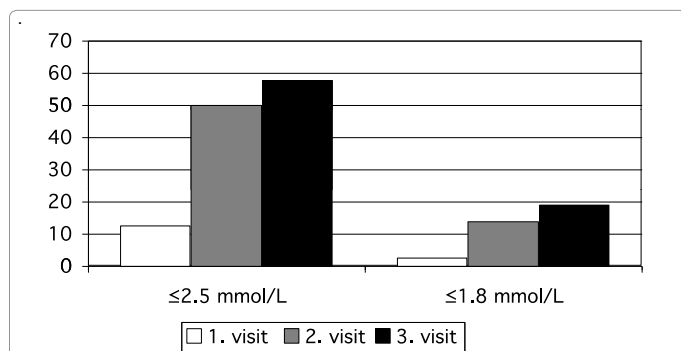


Figure 1: The achievement of 2.5 and 1.8mmol/l LDL-cholesterol goals in the CORVUS study.

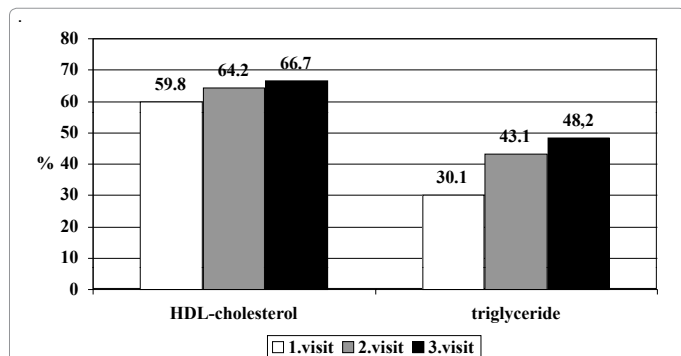


Figure 2: The achievement rate of HDL-cholesterol and triglyceride goals at the 1., 2. and 3. visit.

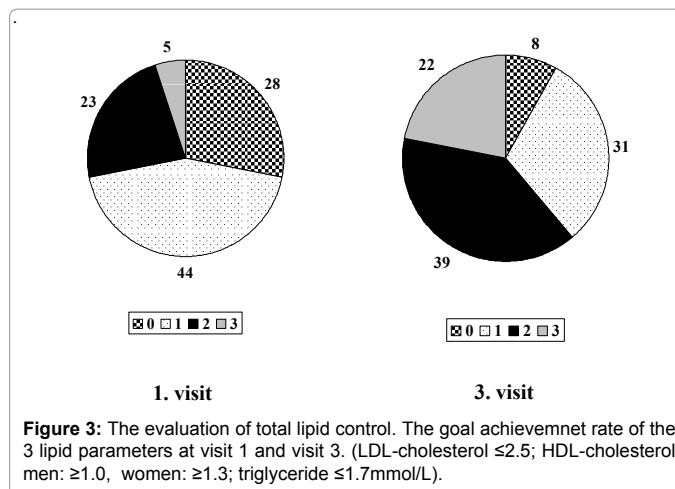


Figure 3: The evaluation of total lipid control. The goal achievement rate of the 3 lipid parameters at visit 1 and visit 3. (LDL-cholesterol ≤2.5; HDL-cholesterol men: ≥1.0, women: ≥1.3; triglyceride ≤1.7mmol/L).

to these. According to the results of these studies the most common reason for failure of target level achievement is that the physicians do not modify the therapy when the patient comes with the laboratory results showing inappropriate lipid levels [10,12]. Results of Fox et al. [16,17] demonstrate that in case of introducing a more efficient statin as lipid lowering therapy, dose titration is less frequently necessary. Considering that therapy modification is often missed in the everyday practice, applying a more powerful statin in the first line is even more to be recommended.

The CORVUS study had the aim to assess the practice of specialists by such a way that during a 3-month period with 2 follow-up visits it recommends a switch to rosuvastatin. The results are clearly hopeful, the rate of achieving LDL cholesterol target level of 2.5mmol/L increased from 12.7% at baseline to 57.7% by the end of the study. This latter one is considered to be quite promising based on Hungarian results published to date (Figure 4) [12,18]. On the other hand, the low value at baseline is not satisfying; nevertheless, the results proved that our colleagues can be encouraged for a better quality of work by periodic assessments. Even after this study 42% of patients remained over the recommended target level. Not to mention that 78% of the entire study population belonged to the very high risk category and the rate of achieving their LDL cholesterol target level of 1.8 mmol/L was only 19% even at the end of study. It is an advantage of our study that unlike in most studies on drugs' effectiveness the rate of achieving 1.8 mmol/L was established not for the entire study population but only for the very high risk group. This relatively low goal achieving rate in the very high risk group underlines the fact, that beside the continuous lipid profile control a higher administration of the combination therapy (i.e. use of ezetimibe) has to be considered [19].

It is to be emphasized that by administration of rosuvastatin which influences favorably all lipid parameters the achievement rate of HDL cholesterol target value and to a lesser extent that of triglyceride (Table 5) and the rate of patients reaching all three lipid parameter target values increased (Figure 3); although all these were not study objectives.

Guidelines recommend in case of vascular disease also more than 50% reduction in LDL cholesterol level in addition to achieving the target values [14,15]. This was realized in our study in 21.1% by visit 3 compared to baseline values measured at visit 1. Based on our data we can only state that regression can be expected at least in so many patients but considering that baseline values measured prior

the introduction of therapy well before entering the study were even higher, the regression of atherosclerosis can be expected in significantly more patients.

Comparison of medicines listed in (Table 2 and 3) clearly shows that the physicians strived for a higher rate of target value achievement, as more and more patients received stronger statin and rate of ezetimibe use increased continuously, too. Based on these result we can state that the administration of high efficient statins is the way of achieving target value. Moreover it is also evident that following this approach, combination therapy, use of ezetimibe can be a great help when striving for higher quality of work [20,21]. It would be more expedient to include in the guidelines that in case of very high LDL cholesterol level the treatment should not be initiated with the lowest dose, as it is to be feared that dose titration may be missed. Advantages of forced titration are proved by studies as well [22].

The occurrence of side effects was very low also in this study. Developing these side effects may not inevitably result in discontinuation of lipid lowering therapy even in the particular patient (dose reduction, a change to another statin or a combination therapy with low dose statin should be considered instead) and must not divert the physician from purposeful, more efficient treatment of the other patients.

The purpose of the CORVUS study was to demonstrate a higher target lipid goal achievement rate among patients at high cardiovascular risk using more potent lipid-lowering treatment options including high-efficient therapies. It proved that a better reduction of lipids can be achieved by the application of rosuvastatin. The target level achievement rate corresponds to the average of CEPHEUS study performed in several European countries (Figure 5) [7]. After further consideration of our results we can conclude that in addition to keeping the importance of prevention on agenda application of registries,

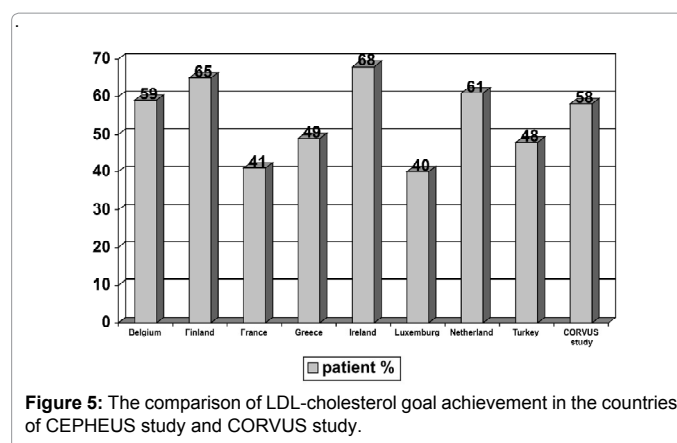


Figure 5: The comparison of LDL-cholesterol goal achievement in the countries of CEPHEUS study and CORVUS study.

educational programs may help the work of colleagues and the optimal lipid lowering treatment of patients.

Declaration of Interest

This material was written independently, and no company or institution supported the authors financially. No professional writer was involved. All authors had full access to all the data in the study, taken responsibility for the integrity of the data and the accuracy of the data analyses, and agreed to the manuscript as written. The authors have given talks, attended conferences and participated in other trials or advisory boards sponsored by various pharmaceutical companies.

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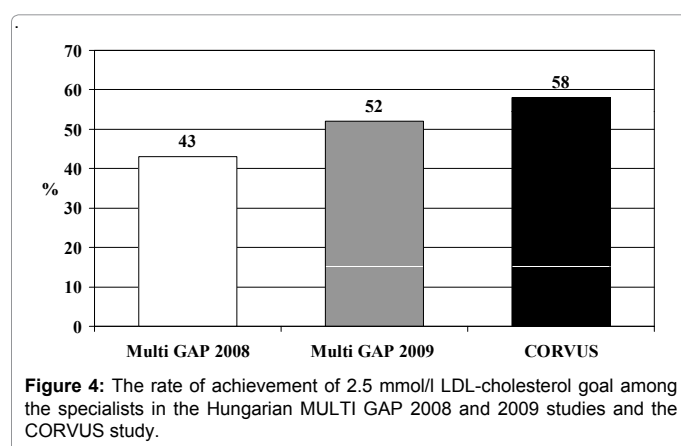


Figure 4: The rate of achievement of 2.5 mmol/l LDL-cholesterol goal among the specialists in the Hungarian MULTI GAP 2008 and 2009 studies and the CORVUS study.

		Visit 1 (n=1077)	Visit 2 (n=1071)	Visit 3 (n=1060)
Total cholesterol	(mmol/L±SD)	6.12±1.29	4.84±1.03	4.51±0.90
LDL-cholesterol	(mmol/L±SD)	3.73±1.12	2.73±0.89	2.44±0.76
HDL-cholesterol	(mmol/L±SD)	1.23±0.34	1.28±0.33	1.19±0.31
Triglyceride	(mmol/L±SD)	2.69±2.37	2.07±1.21	1.94±1.34

Table 5: Lipid levels at each visit in the very high risk group.

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