Statin Therapy in Patients with Type 2 Diabetes Mellitus in Hungary

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Authors' contributions

This work was carried out in collaboration between all authors. Authors LM, IR, GP, IK, Gyula Pados and GJ designed the study, wrote the protocol and completed analysis. Author ZK completed the data entry and managed the statistical analyses of the study. Authors LM and GJ wrote the first draft of the manuscript and managed the literature searches. All authors read and approved the final manuscript.

Original Research Article

ABSTRACT

Aim: The benefit of statin administration in the secondary prevention of cardiovascular diseases in type 2 diabetes mellitus (T2DM) is well documented. The aim of the study was to evaluate the characteristics of lipid lowering therapy and the attainment of target values.
Study Design: Retrospective data analysis.
Place and Duration of Study: Between 2009 and 2011, Hungary.
Methodology: The study was conducted on the patients with T2DM and established cardiovascular events of general practitioners and specialists from the MULTI GAP (MULTI Goal Attainment

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Problem) survey in Hungary using standardized, structured questionnaires. Data collection was performed in 2009 (1582 patients, 55.0% men), in 2010 (1159 patients, 58.4% men) and in 2011 (668 patients, 59.1% men).

Results: In this study all patients received statins, the most frequently used was atorvastatin, followed in 2009 by simvastatin and 2011 by rosuvastatin. Fibrates were taken by 9.3–11.3% of patients and ezetimibe by 8.0–15.9% of patients. The total cholesterol (TC) values in 2009, in 2010 and in 2011 were 5.27±1.23 mmol/l, 4.90±1.30 mmol/l, 4.88±1.29 mmol/l, respectively (p>0.05). The LDL-cholesterol (LDL-C) values were 2.94±1.04 mmol/l, 2.73±0.95 mmol/l, 2.69±1.03 mmol/l, respectively (p>0.05). The proportion of patients at LDL-C target value of <2.5 mmol/l was 35.2%, 42.8%, 47.8% (p<0.001 vs values in 2009) while that of <1.8 mmol/l was 10.6%, 15.9% and 16.8%, respectively (p<0.001 vs values in 2009). There was a linear correlation between the patient compliance estimated by the physicians and the LDL-C achievement rate.

Conclusions: In 2009-2011, a slight improvement in serum cholesterol levels and a significant increase of patients at target TC or LDL-C values were documented among patients with T2DM and cardiovascular diseases. Nevertheless, the authors find very important to improve the quality of lipid lowering treatment in order to increase the number of patients achieving their target lipid values.

1. INTRODUCTION

Cardiovascular disease is a chronic macro-angiopathic complication of type 2 diabetes [1]. The mortality statistics derived from several cross-sectional studies, follow-up surveys and population observation studies of patients with type 2 diabetes mellitus (T2DM) have shown that cardiovascular conditions, mainly myocardial infarction and ischemic stroke, are the leading causes of mortality. Lipid disorders play an important role in the fact that cardiovascular diseases are the most frequent chronic complications in T2DM. As a result, the primary and secondary prevention of cardiovascular events has recently become a significant public health challenge in T2DM [2].

The importance of the secondary prevention of cardiovascular diseases in diabetes is supported by a serie of studies [2,3,4,5,6,7]. It is well documented that in T2DM the occurrence of myocardial infarction is more frequent, mortality in the acute period is higher, and post-infarction late cardiac complications are more common than in patients with a healthy glucose metabolism. It has been shown that in post-myocardial infarction diabetic patients, the occurrence of congestive heart failure related to left ventricle dysfunction (in severe cases cardiogenic shock) and reinfarction rates are higher, and the five year survival rate is lower than in non-diabetics [2,3,4,6].

Haffner et al. [8] in their follow-up study demonstrated that in post-myocardial infarction diabetics the reinfarction rate is approximately twice (45%) that of post-MI non-diabetics (18.8%) or those diabetics who have not previously suffered a heart attack (20.2%). In the OASIS multicenter study, patients with non-Q-myocardial infarction or unstable angina requiring hospitalization were followed for up to two years. In a randomized sample of 8,013 patients, 1,718 (21%) suffered from T2DM. In this group the rate of deaths within hospital was 2.9% and the occurrence of congestive heart failure 12%; in non-diabetics the rates were 2% and 8%, respectively [9]. In T2DM, apart from coronary events, carotid and peripheral arterial disease also have major clinical significance as well. It is the nature of the disease that if atherosclerosis is present in one area, it may be assumed that other areas are also involved.

In T2DM the importance of secondary prevention of cardiovascular diseases is clear. This consists of lifestyle modification and pharmacological therapy. In the latter, lipid lowering treatment is of increasing importance [2]. This involves the lowering of LDL-cholesterol (LDL-C) despite the fact that in T2DM the typical dyslipidaemia is an increase in triglycerides and rate of small dense LDL and a decrease in HDL-cholesterol (HDL-C). The drugs of first choice are statins both in non-diabetics and diabetics. In this study the LDL-C and total cholesterol (TC) goals are those recommended by the 4th Hungarian Cardio-vascular Consensus Conference [10]. In high-risk patients (such as those with T2DM) the levels are 2.5 mmol/l and 4.5 mmol/l, respectively; in very high-risk cases (including patients with T2DM and coronary artery disease) the levels are 1.8 mmol/l and 3.5 mmol/l, respectively [10].

Using data from the diabetic patient subgroup of the Hungarian Multi-Goal Attainment Problem (MULTI-GAP) 2009, 2010, and 2011 studies [11,12,13], this paper aims to analyse the characteristics of lipid lowering, the data on the trend of LDL-C levels and the attainment of LDL-C goals.

2. METHODS

In this study, we analysed the Hungarian MULTI-GAP 2009, 2010, and 2011 survey data collected from patients with T2DM, using structured questionnaires to monitor the effectiveness of lipid lowering therapy among high-risk patients of general practitioners (GPs) and specialists. Further details on the methods and the results of these studies are provided elsewhere [10,11,12,13,14]. During the study, the principles of the Declaration of Helsinki were observed. The research was approved by the Scientific and Research Ethics Board of the Hungarian Ministry of Health and the patients gave their consent to participate.

Risk classification was performed according to the recommendations of the 4th Hungarian Cardiovascular Consensus Conference: patients with T2DM are categorized as high-risk, while diabetic patients with a history of acute coronary syndrome or other vascular event are categorized as very high-risk patients. In the MULTI GAP studies each patient has a documented history of a cardiovascular event and are thus within the very high-risk category [10].

The number of specialists (internists, diabetologists, cardiologists, neurologists) involved varied between 129 and 149, and that of GPs between 53 and 106. The participating doctors were asked to collect the data of the last 10 patients to have suffered from acute coronary syndrome, stroke, transient ischaemic attack (TIA), and/or peripheral arterial disease.

We registered the patients' gender, age, anthropometric parameters, the presence of diabetes and hypertension, smoking habits and certain laboratory parameters (HbA$_{1c}$, fasting and postprandial glucose level, lipid levels), and the patients were asked about their medical cardiovascular prevention treatment. The results of this study were obtained in the same way as those of all MULTI GAP survey [11,12,13,14]. In terms of antidiabetic therapy, the diabetics were asked only about the main groups of drugs

(alpha-glucosidase inhibitors, sulphonylurea derivatives, biguanides [metformin], thiazolidine-diones, insulin, DPP-4-inhibitors). The laboratory data were analysed locally in accredited laboratories. The patients' LDL-C, total cholesterol, HDL-C, and TG levels were available for analysis, the measurements of one patient were made in the same local lab. LDL-C values were accepted regardless of whether they were measured directly or calculated using the Friedewald formula [15], except in cases where the triglyceride levels were above 4.5 mmol/L (400 mg/dL) when only direct measurements were accepted. We also analysed the data of T2DM patients taking statins: There were 1,582 in 2009, 1,159 in 2010, and 668 in 2011 (the proportion of males was 55.0%, 58.4% and 59.1%, respectively).

Data collection was also undertaken to examine patients' compliance. As we had no opportunity to count the number of tablets taken, this was estimated by doctors and was based on the frequency of statin prescription, the patients' knowledge and questioning of the patients. The analysis of patients' compliance was undertaken by pooling the data for the three years.

2.1 Statistical Analyses

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 chi-square test. The Mann–Whitney U test was used for continuous parametric variables. All tests were two-sided, and *p* values < 0.05 were considered statistically significant. Statistical analyses were performed using SPSS 7.5.

3. RESULTS

The most important clinical parameters of patients across the years 2009, 2010, and 2011 were: Age (years) 64.1±9.9, 65.4±9.2, 66.2±9.8; body weight (kg) 87.7±15.7, 87.8±15.7, 86.6±16.4; Body Mass Index (BMI, kg/m^2) 30.2±5.6, 30.6±5.2, 30.6±5.1.

Across the three years examined, the TC and LDL-C values decreased continuously (p > 0.05). Although the target values recommended for high-risk patients (TC <4.5 mmol/l, LDL-C <2.5 mmol/l) and for very high-risk patients (TC <3.5 mmol/l, LDL-C <1.8 mmol/l) were attained to a statistically higher degree, these remained lower

than 50% concerning the goals for high-risk patients and lower than 20% for the very high-risk cases. (As the 2TDM patients in the MULTI GAP studies are in the very high-risk category, the unfavourable latter values should mainly be taken into account). A greater improvement in goal attainment was observed between 2009 and 2010, than between 2010 and 2011 (Table 1).

The value of HbA_{1c} was 7.29±1.09% in 2009 and 7.23±1.17% in 2011 (p = 0.024). The distribution of the HbA_{1c} values is presented in Fig. 1.

Table 1. Serum total cholesterol and LDL-cholesterol and the attainment of target values in patients taking statins with type 2 diabetes mellitus (MULTI GAP 2009, 2010, 2011 studies)

	2009 (n=1582)	2010 (n=1159)	2011 (n=668)
Total cholesterol (mmol/l)	5.27±1.23	4.90±1.30	4.88±1.29
LDL-cholesterol (mmol/l)	2.94±1.04	2.73±0.95	2.69±1.03
The attainment rate of total cholesterol <4.5 mmol/l (%)	24.3	38.4*	40.4*†
The attainment rate of total cholesterol <3.5 mmol/l (%)	6.0	11.5*	12.0*
The attainment rate of LDL-cholesterol <2.5 mmol/l (%)	35.2	42.8*	47.8*‡
The attainment rate of LDL-cholesterol <1.8 mmol/l (%)	10.6	15.9*	16.8*

p<0.001 versus value of 2009; †p<0.05 versus value of 2010; ‡p<0.01 versus value of 2010
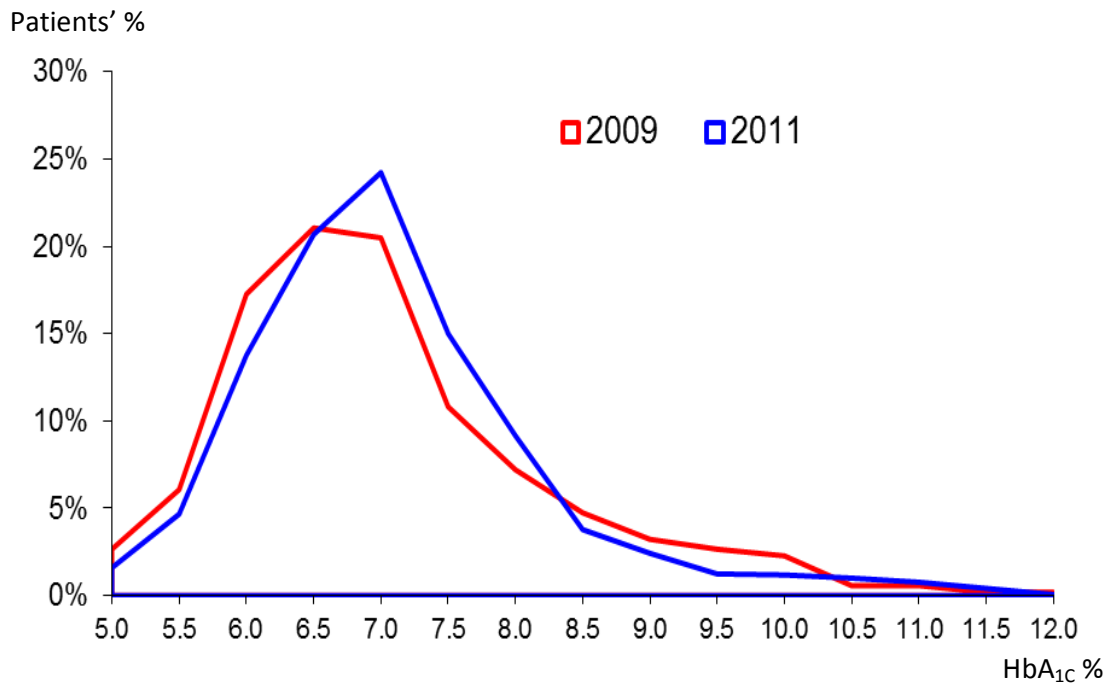

Fig. 1. Distribution of HbA_{1c} values in patients with type 2 diabetes mellitus participating in the MULTI GAP study in the years 2009 and 2011

There was a linear correlation between the estimated patients' compliance, i.e. their willingness to cooperate in drug taking, and the achievement of 2.5 mmol/l LDL-C target value (Fig. 2).

The most frequently used statin in 2009 was atorvastatin, followed by simvastatin and rosuvastatin (mean daily doses of 33.8 mg, 31.0 mg and 18.2 mg, respectively). By 2011, a remarkable change had occurred: in second place after atorvastatin (mean daily dose 32.9 mg) was rosuvastatin (mean daily dose 19.5 mg), followed by simvastatin (mean daily dose 19.8 mg). Fibrates were taken by 9.3–11.3% of patients and ezetimibe by 8.0–15.9% of patients (Fig. 3).
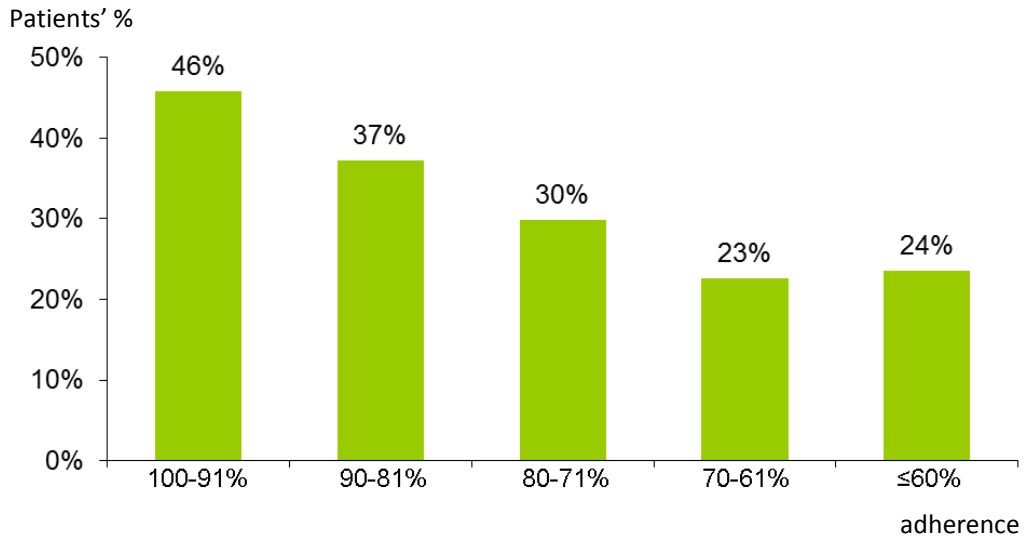

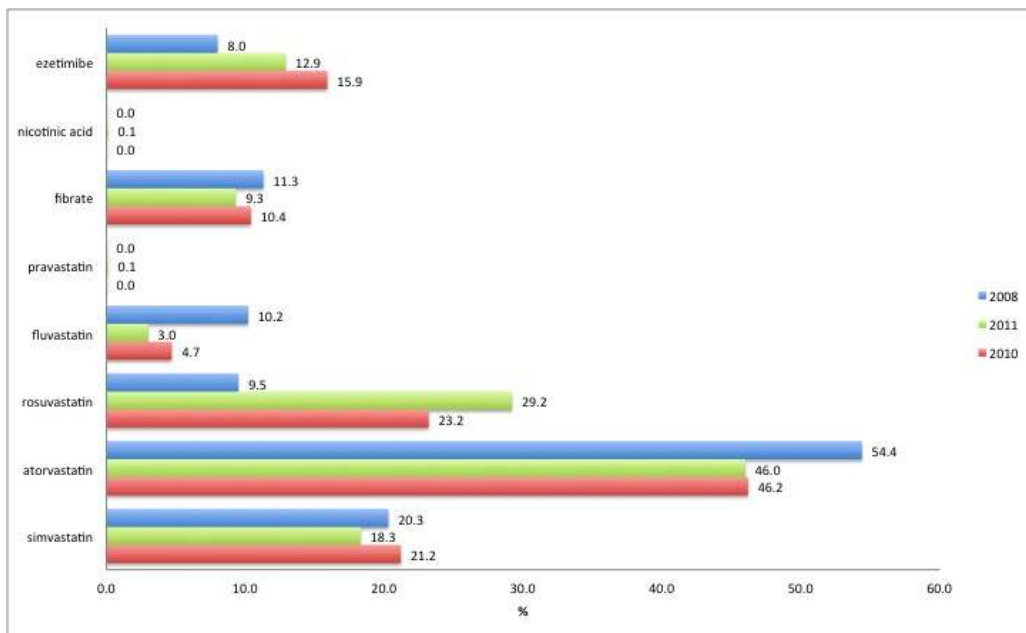**Fig. 2. Correlation between estimated patients' compliance and goal attainment rate (pooled analysis for three years)**

Fig. 3. The distribution of lipid lowering therapy in patients with type 2 diabetes mellitus in 2009, 2010, and 2011

4. DISCUSSION

In the prevention of cardiovascular disease in patients with T2DM, the attainment of the LDL-C target value assessed by guidelines is of very great importance. Triglyceride and HDL-C levels are also relevant, but their values as treatment goals are less significant. Recently, the level of non-high-density lipoprotein cholesterol (non-HDL-C) has been defined as an additional treatment target, secondary to LDL-C, especially in conditions associated with high triglyceride levels such as T2DM. Nevertheless, the use of non-HDL-C has not yet become part of routine practice [16,17].

As for the treatment goals, we have taken into consideration the recommendations of the 4th Hungarian Cardiovascular Consensus Conference [10], which are similar to and based on those of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), and the joint recommendations for the treatment of dyslipidemias by the European Society of Cardiology, the European Atherosclerosis Society (ESC/EAS) and the International Society of Atherosclerosis [18,19,20].

The priority of statin therapy in T2DM patients is indisputable [2,21] As the LDL-C and TC values are high in most diabetics, the use of statins is indispensable. In T2DM cases, doctors do not have to explain why they administer statins, rather they should explain why they do not. In this study all patients received statins. We analysed separately the attainment rate of lipid goals for high-risk patients (TC <4.5 mmol/l, LDL-C <2.5 mmol/l) and for very high-risk patients (TC <3.5 mmol/l, LDL-C <1.8 mmol/l). The less strict high-risk lipid goals are recommended for patients with atherosclerotic disease (coronary, carotid or peripheral) or patients with T2DM. In this study, all patients were in the very high-risk category as, besides having T2DM, an atherosclerotic event had also occurred (this was an inclusion criterion). Between 2009 and 2011 a decreasing tendency could be observed in LDL-C and TC levels and the rate of patients achieving lipid goals increased. However, despite the improvement in the quality of the treatment, the high-risk lipid goal attainment rate was less than 50%, and that of the very high-risk goals was critically less than 20%. In contrast, glycaemic control was acceptable (mean HbA_{1c} values 7.29–7.23%).

What could be the reason for the only modest improvement derived from the statin therapy? This is not specific to diabetes but is common in other MULTI GAP analyses [11,12,13,14]. In most cases three statins were administered, the effectiveness of which is supported by a series of studies. In the period analysed, use of the most potent statin, rosuvastatin, became more frequent. In relation to increasing doses, we ascertained that only a slight improvement could be obtained by this means. It is well known that by doubling the statin dose an additional 5–7% lowering of LDL-C could be expected [22]. The ezetimibe proved to be an efficient drug not only n lowering LDL-C but in the reduction of the clinical events too [23]. Its more frequent use of would be another possible source of further improvement [24,25].

The most important reason for the failure to derive better results from treatment could be patients' compliance. Our data suggest that greater willingness to cooperate can significantly improve the goal attainment rate. Recently we have shown that persistence in taking statins in Hungarian patients is very poor: At 12 months only 26.3% of T2DM patients were taking the statins prescribed [26,27]. To improve the patients' persistence have accentuated importance.

The clear advantages of statin administration in relation to the cardiovascular endpoints and mortality are unquestionable. The potential side effects are also well known and these include the worsening of glycaemic control, an increased rate of new onset diabetes [28,29,30,31,32,33]. However, we agree with the opinion that overall the favourable effects outweigh the harmful effects [21,31]. This is the present standpoint of the U.S. Food and Drug Administration (FDA) [34]. The use of statins in patients with T2DM is a crucial aspect of secondary cardiovascular disease prevention. We suppose that their administration has played an important role in the fact that life expectancy in Hungary increased by 5.33 years from 1993 to 2010, of which 2.39 years were accounted for by a decrease in cardiovascular mortality [35,36] and this occurred despite an increase in the prevalence of some other cardiovascular risk factors such as obesity and T2DM [37,38].

5. CONCLUSION

Administration of statins is the crucial part of lipid lowering therapy in patients with T2DM and

cardiovascular diseases. Between 2009 and 2011 a slight improvement in serum cholesterol levels and a significant increase of patients at target TC or LDL-C values had been detected. Statin use shifted towards the most portent atorvastatin and rosuvastatin. Despite these favourable changes a continuous need remains for more effective lipid lowering treatment in order to increase the rate of patients with target lipid values.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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