

Full Length Research Paper

Utilization of lipid modifying agents in the Karvina district: A comparison with the Czech Republic, 2002 to 2009

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The objective of this study was to evaluate the structure and development of consumption of hypolipidemic agents. Data concerning utilization of individual hypolipidemic drugs from 2002 to 2009 were obtained from the State Institute for Drug Control database and General Health Insurance Company, Karvina district database. Utilization of hypolipidemic drugs were stated in DDDs in correspondence with the anatomical therapeutic chemical (ATC) classification, and the costs in CZK. Information on utilization is expressed in the number of DDD per 1,000 inhabitants per 1 day (DID). The utilization of fibrates slightly decreased, while statins increase from 13.55 DID (2002) to 60.10 DID (2009) was observed. The total utilization of hypolipidemic drugs in DID have been continuously increasing (32.34 DID in 2002, 76.30 DID in 2009). In the compared data from the Karvina district, an increased utilization of fibrates and decreased utilization of statins were observed. The most significant difference was noted in the utilization of ezetimibe (the utilization of which from 2006 to 2009 was 2 to 3 times higher than was the average in the Czech Republic). Increasing availability of hypolipidemics was noticed with some regional discrepancies and sex differences in consumption of this group of medicines.

Key words: Utilization of medicinal products, lipid modifying agents, hypolipidemic drugs, statins, fibrates, ezetimibe.

INTRODUCTION

Despite the positive trend in the recent years, diseases of the circulatory system have been the most frequent cause of death both in women and men in the Czech Republic (Table 1). In women, the ischemic heart disease mortality is the highest, followed by atherosclerosis as the

second in sequence, while in men these diseases rated on the first and fourth positions. At the same time, it must be said that in case of this group of diseases, there has been the most noticeable decrease within the last 20 years (Czech Health Statistics Yearbook: Death 2002 to 2009).

Hypolipidemic therapy expenses are not inconsiderable, although there has been a substantial cut in prices, especially in case of drugs from the group of statins. The use of statins in both primary and secondary

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Table 1. Standardized mortality ratio of diseases of the circulatory system in the Czech Republic (Czech Health Statistics Yearbook: Death 2002 to 2009).

Year	%
2002	52.8
2003	52.2
2004	51.4
2005	52.0
2006	50.3
2007	50.1
2008	49.8
2009	50.4

prevention has been supported with numerous clinical studies and meta-analysis which have proved a significant decrease of cardiovascular morbidity and mortality in a group of patients treated by means of these substances. In regards to the long-term character of the treatment and its costs, the efficiency of this therapy has been being discussed (Bartas and Kolář, 2008a).

The use of hypolipidemic drugs in the Czech Republic (and the former Czechoslovakia) has been influenced, to great extent, by the lack of availability of some drugs prior to the year 1989. The availability of foreign medicinal products was limited at first, or with substantial delays. In case of the hypolipidemic drugs group, the radical shift followed the introduction of statins which represented a dramatic change in the extent and effectiveness of the hypolipidemic therapy (the first statin was authorized in the Czech Republic only in 1989). This group of hypolipidemic drugs is currently the most frequently used group at the expense of earlier drugs from the group of fibrates and bile acid sequestrants. The following time period shows a visible trend of gradual change in prescription of statins converging to the state which is common in advanced countries. This situation required the rise of costs of this therapy and this financial issue led also to certain regulation in prescription of these drugs which would ensure sustainability of the rising costs. The increased utilization of hypolipidemic drugs was accompanied by a reduction in costs of this group, especially owing to the rivalry among individual drugs and the reduction of health insurance reimbursements. Nevertheless, the total prescription of statins remained lower than in the majority of advanced countries: 70 DID in the Czech Republic (2010), 72 DID in Sweden (2010), 88 DID in Finland (2009), 110 DID in Norway (2010), and 123 DID in Australia (2008) (Bartas and Kolář, 2008a).

As far as the used medications are concerned, no significant worldwide changes have been observed within the last decade in the range of used substances with the exception of ezetimibe, that is, the first selective cholesterol absorption inhibitor with the indication of homozygous familiar hypercholesterolemia and primary

hypercholesterolemia, and introduction of the most effective lipid-lowering substance niacin back into the therapy (in combination with laropirant - the selective antagonist of prostaglandin receptors) (Parhofer, 2009). Statins remain the most essential group of drugs. Their overwhelming majority is very well tolerated and their side effects are well documented. The most serious side effect is myopathy, especially its rare fatal manifestations (Lewis, 2011). Statins have thus been playing their role not only in secondary but also primary prevention (Aalbers, 2011). In connection with statins, the recently highly debated diabetogenic effect of statins ought to be mentioned. The JUPITER study recorded an almost 20% increased risk of type 2 diabetes in patients treated with rosuvastatin. Although the latest meta-analysis of randomized studies of statins reduced the risk to 9%, attention is being paid to this issue (Long et al., 2011). It can be said that the latest development and introduction of new hypolipidemic drugs on the market were more of a disappointment (cerivastatin and its withdrawal from the market, torcetrapib the development of which was halted virtually before its approval by FDA and introduction on the market in 2006, the latest results of studies on ezetimibe – according to the ENHANCE study its taking does not impede the progress of atherosclerosis in the carotid area) (Brown and Taylor, 2008).

The results of the SHARP study, however, proved the benefit of the combination ezetimibe + simvastatin during which significant reduction of the risk of serious atherosclerotic and vascular incidents was recorded (Sharp collaborative group, 2010; Mikhailidis et al., 2011). The standard hypolipidemic therapy has thus remained the approved statin pharmacotherapy supplemented with fibrates in appropriate indications, in case of severe forms of homozygous familiar hypercholesterolemia supplemented with medium dosages of bile acid sequestrants (very good effect during diet measures compliance), or alternatively the use of combination niacin + laropirant (Bartas and Kolář, 2008a). Niacin is designed for a group of patients in which LDL (low density lipoprotein) cholesterol target levels were not achieved or in which the HDL (high density lipoprotein) cholesterol values are considerably low (Hochholzer et al., 2011).

It must be mentioned that the results of studies monitoring the effect of statin + fenofibrate combination are contradictory. While the ACCORD study discovered that this combination does not reduce cardiovascular risks in diabetes 2 high risk patients (The ACCORD study group, 2010), another study described a higher effect of the fenofibrate + statin combination in comparison with monotherapy and thus confirmed the advantage of the use of fenofibrate in metabolic syndrome therapy during which the glycemia reduction occurs on an empty stomach (Bays et al., 2010).

The position of simvastatin and atorvastatin is noticeably prominent in the statin group. Recently, there

has been an apparent shift from simvastatin to atorvastatin; such a trend is evident in the Czech Republic as well but with a certain delay in comparison with other countries. In Ireland, for example, the shift towards atorvastatin occurred between 1998 and 2002. The position of rosuvastatin (which, according to the SATURN study results, possesses apparently the most optimum effect spectrum) has been growing stronger abroad. However, rosuvastatin was not commonly used in the Czech Republic within the monitored time period on account of prescription limitations, and which was released only in 2011.

Attention has been lately paid not only to the existing procedures: reduction of the LDL cholesterol and triglyceride levels, but also to the increase of HDL cholesterol. Apart from fibrates, its concentration can be influenced also by glitazars and cholesterylester transfer protein (CETP) inhibitors. In this context, anacetrapib seems to be very promising; it is a substance with so far the highest effect on the HDL cholesterol level (Cannon et al., 2010). There have been efforts of preparation of apolipoprotein A1 (ApoA1) by means of recombinant techniques (Davidson, 2011). The research has, nevertheless, been directed in other ways as well, for example the ApoA1 Milano infusion, ApoA1 mimetics, stimulation of ApoA1 production and ACAT inhibitors (cholesterol esterification inhibitors) (deGoma and Radee, 2011). More attention has been paid also to plant sterols and their use in so called "functional foods". The use of plant sterols in prevention of ischemic heart disease has been supported by results of numerous clinical studies which have indicated that their regular intake in dosages from 800 to 1000 mg per day significantly lowers the LDL cholesterol levels and has further positive effects (antioxidant, anti-inflammatory, antimycotic etc.) (Bartas and Kolář, 2008b).

The positions of statins will probably remain predominant and their indication spectrum may broaden (prevention of the Alzheimer's disease and cerebrovascular accidents) (Bartas and Kolář, 2008a). Preference can be given to combinatory treatment for several reasons – first of all, majority of patients do not suffer from an isolated disorder of lipid metabolism, but a combination of deviations. Another reason is the fact that only in some patients optimal lipoprotein level can be achieved by monotherapy. The CRUCIAL study proved the advantage of a fixed combination amlodipine / atorvastatin during which a more noticeable decrease of the ischemic heart disease according to the Framingham cardiac risk score was accomplished than were the results of the ordinary therapy (Zamorano et al., 2011). More clinical studies of statins have been under way. It will also be interesting to observe whether in other countries, similarly to Great Britain since 2004, for example, a shift into the category of OTC drugs in case of some statins occurs (Bartas and Kolář, 2008a). The important figure from the point of view of therapy

efficiency is whether target values of LDL cholesterol are achieved in patients treated with hypolipidemic drugs.

According to the latest recommendations, the target LDL cholesterol values are as follows: < 3 mmol/l in general public, < 2.5 mmol/l in individuals without a cardiovascular disease with type 1 or type 2 diabetes, and < 2 mmol/l in individuals with a cardiovascular disease (Vaverková et al., 2007).

The STEP study conducted in the Czech Republic in 2010 discovered that only in a half of the patients treated with statins the target values are achieved; in case of people with a high cardiovascular risk it is only in 20% (Hradec, 2011). Similar results were found out also in American diabetics with the target LDL cholesterol values achieved in only a half of them (Kuznik and Mardekian, 2011). The lipid lowering agents belong to the second most common pharmacologic agents prescribed for individuals with metabolic syndrome (Gharipour et al., 2011). Considering the fact that hypolipidemic drugs have been used by a continuously increasing number of patients, largely for a long time period and despite some potentially dangerous health states which can occur during the therapy, the importance of an appropriate compliance and adherence of treated patients has been growing. The data indicate that adherence generally increases in polymorbid patients, but at the same time declines with increasing age (Pedan et al., 2007). It is stated that only 60% of patients over the age of 75 know what prescribed medicine they take and only 21% are aware of the consequences of non-compliance (Strojil et al., 2005). Gender also influences the degree of adherence, higher adherence values are accomplished in women (Mann et al., 2010). This is the reason for the importance of cooperation between pharmacists and doctors, thereby making it possible to substantially influence further efficiency of the therapy at its very beginning (Pedan et al., 2007). Thus, the objective of this study was to evaluate the structure and development of consumption of hypolipidemic agents in the Czech Republic in context to regional differences.

METHODOLOGY

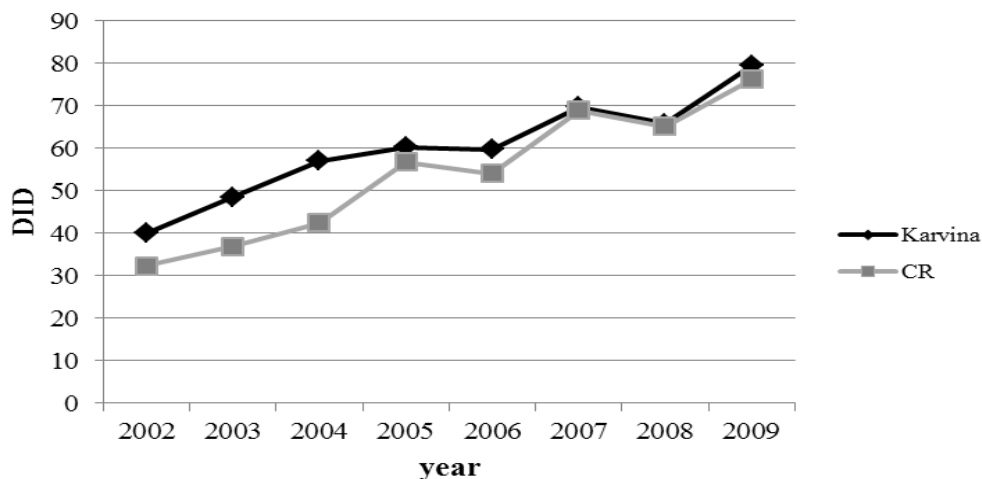
Data concerning utilization of individual hypolipidemic drugs from 2002 to 2009 were obtained from the database of General Health Insurance Company in the Czech Republic (GHIC CR). They also include total dispensation information on medications from the hypolipidemic drugs group which were realized in pharmacies by persons insured with the GHIC CR in Karvina district. The figures presented by the health insurance company included numbers of dispensed packages of individual medications, information on the gender and age groups of individual medication users, as well as the amount of payment of particular dispensed medications (in CZK). The utilization of both the individual hypolipidemic drugs and the groups are stated in absolute values in DDD in accordance with the ATC/DDD system, while the relative values of utilization in the number of DDD for 1,000 individuals per day (DID) and expenses are stated in CZK. The DDD values correspond with those of the WHO methods from 2009 (Table 2). The obtained data were

Table 2. Defined daily doses of statins by the WHO (in mg).

ATC code	INN name	Defined daily dose	
		Until 2009	Since 2009
C10AA01	Simvastatin	15	30
C10AA02	Lovastatin	30	45
C10AA03	Pravastatin	20	30
C10AA04	Fluvastatin	40	60
C10AA05	Atorvastatin	10	20
C10AA07	Rosuvastatin	10	10

Table 3. Consumption of hypolipidemic agents in the Czech Republic between 2002 and 2009 (in DID).

Year	Statins	Fibrates	Bile acid sequestrants	Ezetimibe	Total
2002	13.5511	18.7476	0.0453	0.0000	32.3440
2003	18.0240	18.8063	0.0434	0.0000	36.8737
2004	24.5495	17.8795	0.0403	0.0000	42.4693
2005	35.8053	20.6026	0.0246	0.3381	56.7705
2006	37.6090	15.8244	0.0227	0.5872	54.0433
2007	51.0950	17.0146	0.0249	0.8240	68.9585
2008	50.6025	13.7491	0.0242	0.8554	65.2312
2009	60.0987	15.0482	0.0247	1.1292	76.3008

**Figure 1.** Total consumption of hypolipidemic agents.

compared with data on the utilization of hypolipidemic drugs in the Czech Republic which were adopted from the AISLP program of the Infopharm Company, the primary source of information being figures published by the State Institute for Drug Control (SIDC).

RESULTS

The utilization of hypolipidemic drugs in Czech Republic had an increasing tendency (32.34 DID in 2002 to 76.30

in DID 2009) (Table 3, Figure 1). The expenses of hypolipidemic drugs rose from CZK 2.097 billion in 2002 to CZK 2.818 billion in 2009 (with the maximum of CZK 3.003 billion recorded in 2005). As far as the individual groups of medications are concerned, the highest rise was recorded in the groups of statins (13.55 DID in 2002, 60.10 DID in 2009) (Figure 2), while in the group of fibrates there was a slight decrease (18.75 DID in 2002, 15.05 DID in 2009) (Figure 3). The utilization of bile acid sequestrants has a continuously falling tendency,

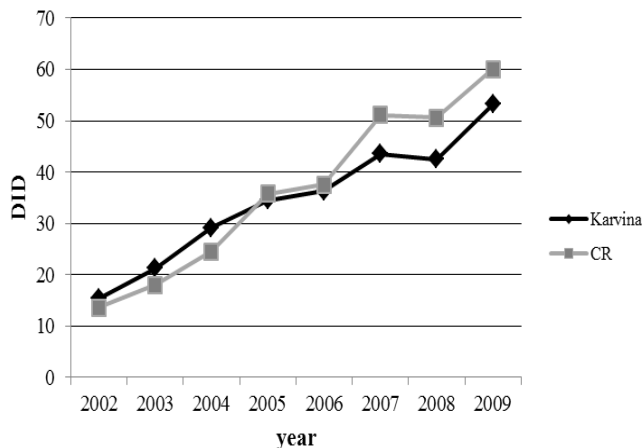


Figure 2. Consumption of statins.

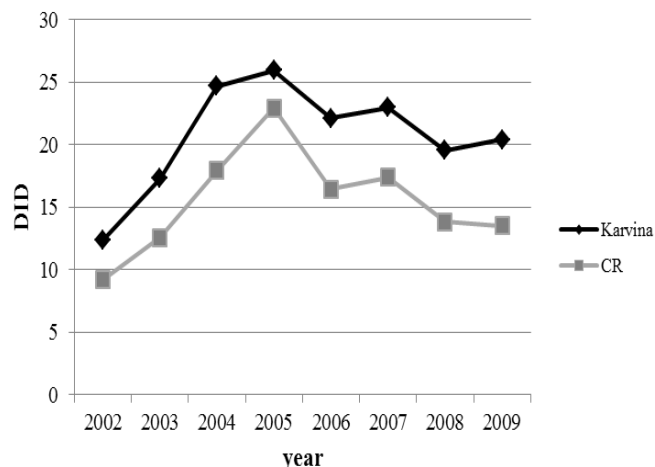


Figure 5. Consumption of simvastatin.

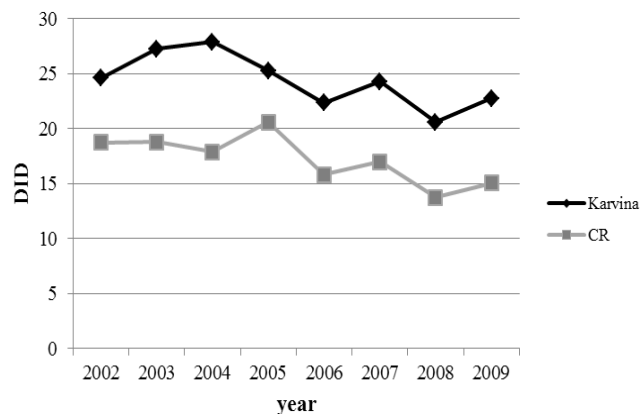


Figure 3. Consumption of fibrates.

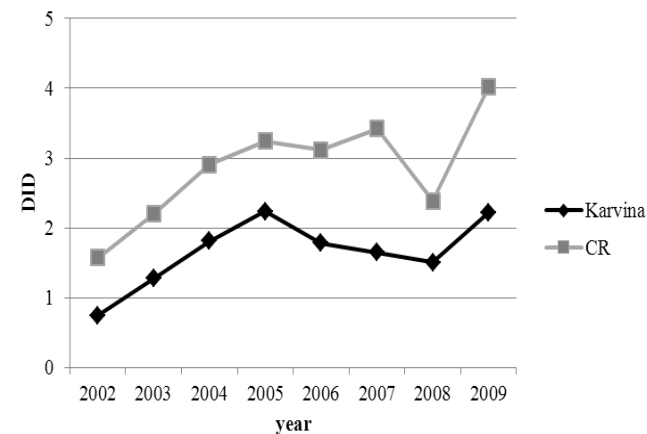


Figure 6. Consumption of fluvastatin.

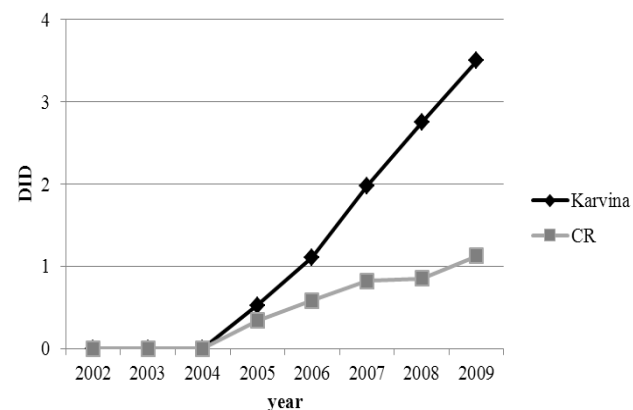


Figure 4. Consumption of ezetimibe.

however, they represent only an insignificant portion of the overall utilization of hypolipidemic drugs (0.0453 DID

in 2002, 0.0247 DID in 2009). Ezetimibe utilization has a rising tendency (0.34 DID in 2005, 1.13 DID in 2009) (Figure 4).

In case of evaluation of utilization of individual active substances from the group of statins, it is possible to divide them into a group in which decrease in utilization was recorded – lovastatin (1.00 DID in 2002, 0.62 DID in 2009), pravastatin (0.504 DID in 2002, 0.004 DID in 2009), and into other statins in the utilization of which an increase was monitored – simvastatin (9.21 DID in 2002, 13.52 DID in 2009) (Figure 5), fluvastatin (1.58 DID in 2002, 4.02 DID in 2009) (Figure 6), and especially atorvastatin in case of which the increase was the most significant (1.26 DID in 2002, 39.64 DID in 2009) (Figure 7). This development resulted in the fall of DDD price; in case of the most-widely spread atorvastatin the most significant drop in the price was observed in the monitored time period (Figure 8).

Information on utilization in the Czech Republic was

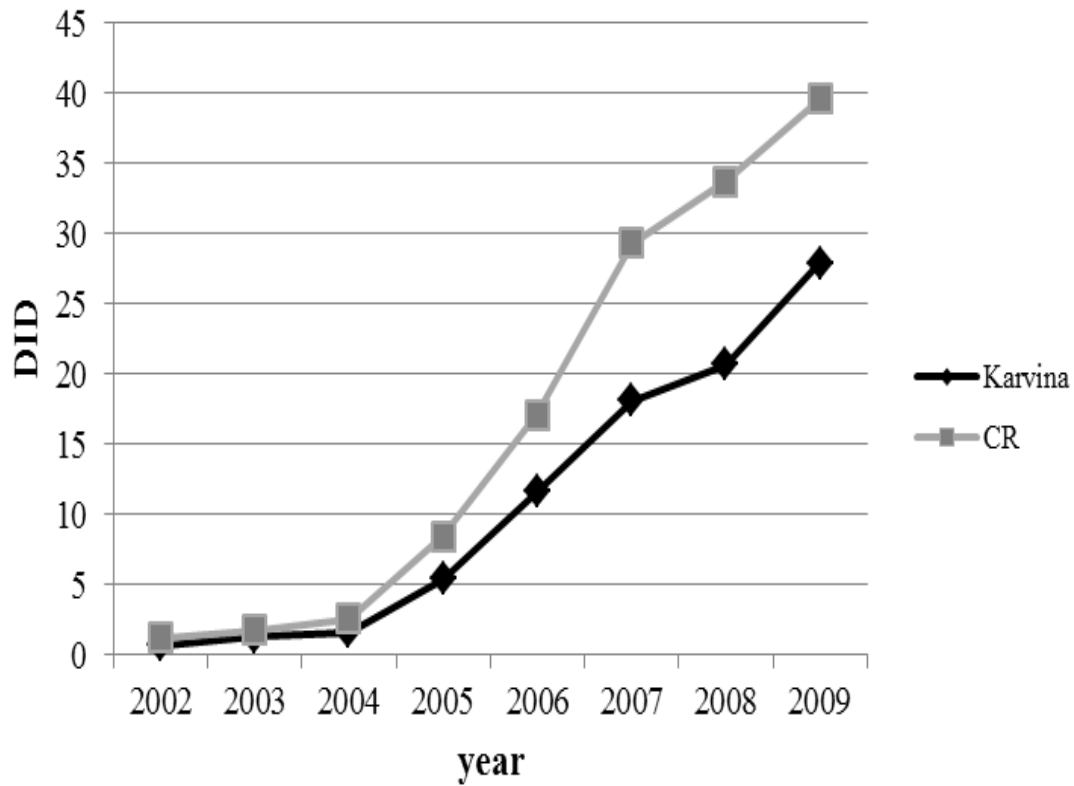


Figure 7. Consumption of atorvastatin.

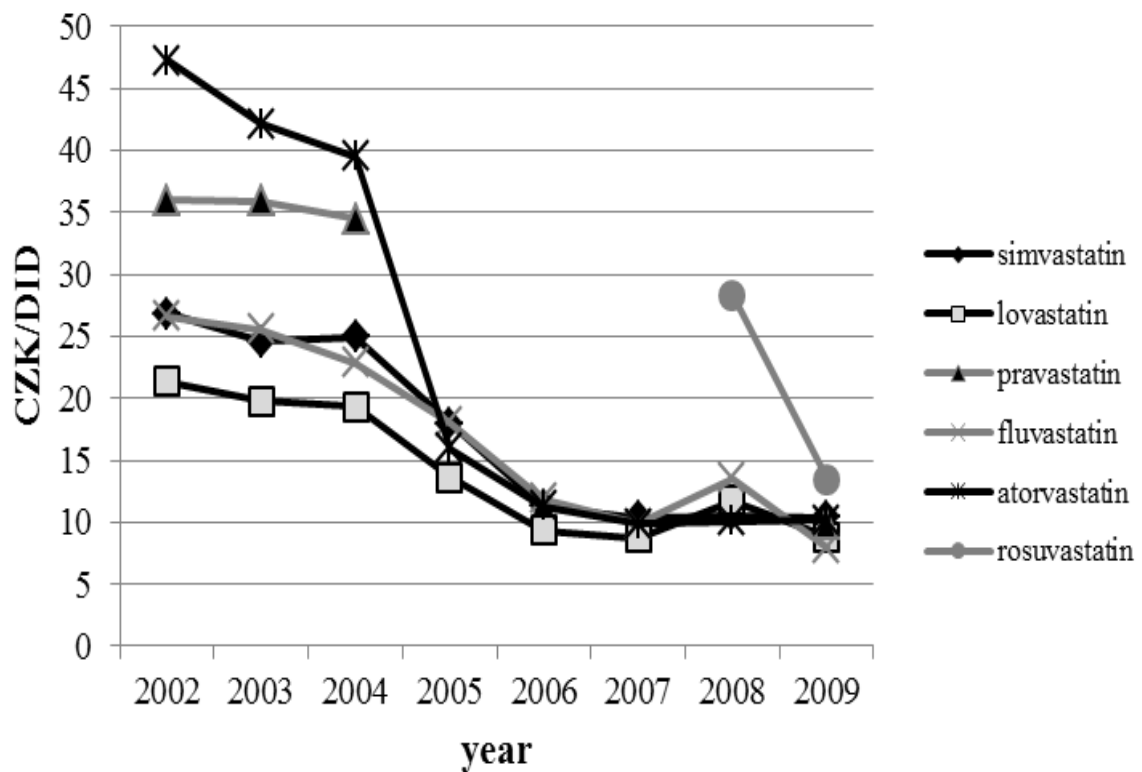
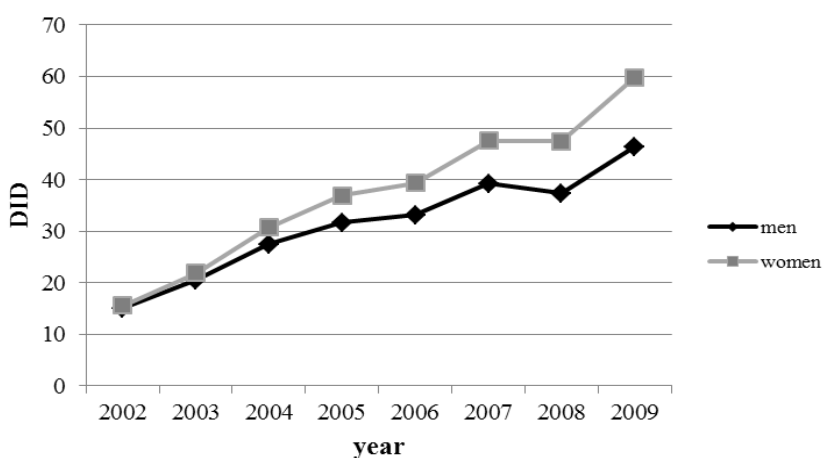


Figure 8. Development of the statins prices (by SIDC).

Table 4. Consumption of hypolipidemic agents in Karvina district (Czech Republic) between 2002 and 2009 (in DID).

Year	Fibrates	Statins	Other	Total
2002	24.6140	15.3580	0.0290	40.0010
2003	27.2840	21.2740	0.0250	48.5830
2004	27.8910	29.1790	0.0320	57.1020
2005	25.2950	34.4590	0.5370	60.2910
2006	22.3380	36.3450	1.1270	59.8100
2007	24.2830	43.5150	2.0030	69.8010
2008	20.5870	42.5100	2.7710	65.8680
2009	22.7590	53.1670	3.5240	79.4500

**Figure 9.** Consumption of statins by sex (Karvina district, Czech Republic).

compared with that obtained from the aggregate of persons insured with the GHIC CR in the Karvina district. The GHIC CR is the prominent health insurance company in the Czech Republic. There are 274,000 inhabitants in the Karvina district; the monitored sample comprised approximately 110,000 of insured persons (119.9 thousand in 2002, 95.5 thousand in 2009). The acquired results showed similar tendencies in the development of utilization of individual hypolipidemic drugs as did the compared data about Czech Republic. In contrary to the figures obtained from the State Institute for Drug Control, the data presented by the health insurance company render the possible comparison between genders. Moreover, due to the fact that they stem from real prices, they bring more accurate information on therapy expenses, unlike the data from the State Institute for Drug Control in case of which the final prices are calculated to the maximum additional margin.

DISCUSSION

There are certain regional differences in the details. The

utilization of statins in Karvina from 2002 to 2009 was slightly higher than was the average figure for the Czech Republic (Figure 4), however, in the years to follow the situation was the other way around. The most significant difference was recorded in fibrates the utilization of which was noticeably higher in Karvina than in the Czech Republic during the whole of the monitored time period (Figure 5). The most striking difference was observed in ezetimibe, in which case the difference between the average utilization in Karvina and the Czech Republic was growing (in 2009 it was three times higher in Karvina than in the Czech Republic) (Table 4, Figure 4). The difference in statins utilization between genders grew continuously larger in the monitored time period. The higher atherosclerosis mortality rate in women could indicate the probability of a higher incidence of this disease in women (Figure 9).

In the course of the monitored time period, there was an increase in the portion of statins in the overall utilization of hypolipidemic drugs, especially at the expense of fibrates the overall utilization of which remained rather invariable (Figure 10).

Utilization of fibrates remained rather steady despite a

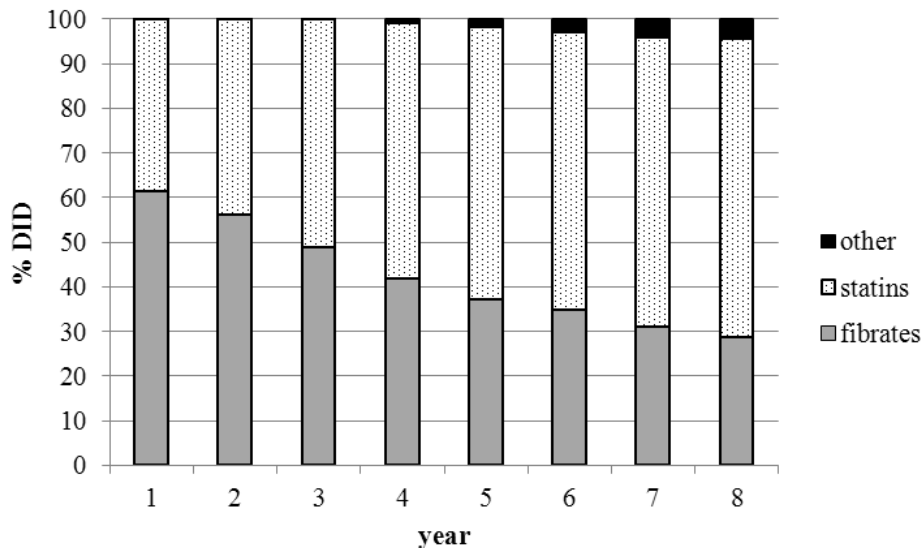


Figure 10. Percentage of drug groups on the total consumption of hypolipidemic agents in Karvina district, Czech Republic (in DID).

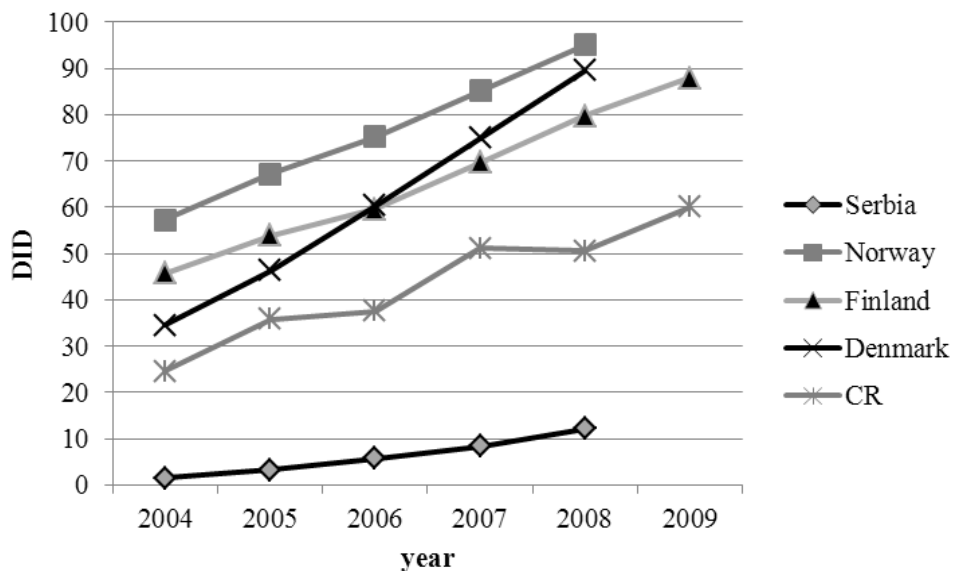


Figure 11. Comparison of statins consumption development in selected countries (Sabo et al., 2011; Prokeš and Suchopár, 2010).

certain decreasing tendency, similarly to the results of a study comparing the use of fibrates in the USA and Canada (in the USA, there was a more significant decline at the expense of statins than in Canada; in Canada, contrary to the USA, generic drugs are widely used, which is the reason for notably lower costs than in the USA) (Jackevicius, 2011).

The utilization of statins in both the Czech Republic and Karvina recorded a continuous growth, similar to other countries (Figure 11). Although the overall utilization of

statins is slightly lower in regards to the fact that the use of fibrates is less common in foreign countries, the general saturation by hypolipidemic drugs is not significantly different than elsewhere. The arrival of statins in general followed by more modern medications (atorvastatin, rosuvastatin) was only a little delayed in Czech Republic than in Western Europe; however, the differences have been evening up fast (in 2010: Sweden 72 DID, Czech Republic 70 DID). When comparing the utilization of individual statins, there is an obviously

Table 5. Share of hypolipidemic agents on the total cost of medicines in the Czech Republic between 2002 and 2009 (in billions of CZK and in %).

Year	Hypolipidemic agents	Medicines in total	Share of hypolipidemic agents (%)
2002	2.097	48.032	4.4
2003	2.392	52.216	4.6
2004	2.959	56.996	5.2
2005	3.003	64.569	4.7
2006	2.117	58.971	3.6
2007	2.525	67.164	3.8
2008	2.451	72.752	3.4
2009	2.819	79.746	3.5
Total	18.440	583.080	3.2

higher conservatism of doctors in Karvina (which corresponds to a higher degree of the use of fibrates); increased utilization of simvastatin and lower utilization of fluvastatin and atorvastatin was observed. Regional differences in utilization were detected even in studies from Norway (Hartz, 2006) and Portugal (Teixeira, 2007).

When comparing data on utilization of statins with the results of a study conducted in Serbia (the highest mortality rate due to ischaemic heart disease in Europe) and in Scandinavia it is clear that the utilization of statins rose in all the monitored countries. Contrary to the linear growth in the monitored countries, the impact of regulatory interventions of 2005 and 2007 is evident, during which the utilization increase of these drugs was retarded. The comparison with results of some earlier studies is complicated especially by the fact that since 2009 new DDD in statins with the exception of rosuvastatin were used. The situation development in the Czech Republic is to a certain extent very similar to that in Portugal where a substantial rise in the use of hypolipidemic drugs (of statins predominantly) occurred, nevertheless, at the same time an overall fall in expenses of this group of drugs was observed due to the introduction of generic drugs (Teixeira, 2007).

The share of hypolipidemic drugs on the overall expenses of drugs had a growing tendency at first (maximum was reached in 2005, probably as a consequence of prescription release of atorvastatin), in the latest time period, however, there is a falling tendency (Table 5). In 2008 and 2009, the therapeutic spectrum of rosuvastatin was broadened. The use of fibrates decreases within the past few years although some studies confirm their beneficial effect especially in metabolic syndrome patients.

When evaluating the obtained outcomes, it is necessary to consider certain limitations resulting from different methodology of the employed data. Information on utilization provided by the State Institute for Drug Control comes from distributors. The data presented by the health insurance company include medications which

were accounted for to the health insurance company and thus indeed dispensed to patients. The health insurance company costs of drugs further include prices of payments for settled medications. They are thus the actual costs of these medications paid for by the health insurance (they do not include prospective participation - additional charges). Most of the medications from the group of hypolipidemic drugs were fully covered by the health insurance company. Contrary to that, the State Institute for Drug Control calculates the prices of dispensed drugs to the maximum additional margin. It is for this reason that the stated costs do not correspond to the actual costs and are overestimated. The comparison of utilization of statins with other foreign data is rather complicated by the fact that since 2009 DDD values have been revised in accordance with the WHO methodology and, with the exception of rosuvastatin, their values were increased. The figures on utilization of combined medications were in the case of the health insurance company (and contrary to the data presented by the State Institute for Drug Control) included according to the individual active substances into the overall uses.

Conclusion

Expenses of hypolipidemic therapy do not evince a notably growing tendency in the past years. The range of patients treated by means of these drugs expands. The specific of the Czech Republic is a still rather high utilization of fibrates which are virtually not used in some other countries. A significant increase in utilization of hypolipidemic drugs in the Czech Republic occurred in the monitored time period. This increase was noticeable in the groups of statins, however, when it comes to other hypolipidemic drugs, an evident decrease or over stagnation can be noticed. There was no any rise in the expenses of hypolipidemic therapy within the monitored time period though, due to the increase in the price (lower payments via health insurance, introduction of generic

drugs). Such changes allowed for a treatment of growing numbers of patients. Due to the current loosening of prescription regulations the Czech Republic approximated substantially more advanced countries.

Abbreviations: **ACCORD**, Action to control cardiovascular risk in diabetes study; **ATC**, anatomical therapeutic chemical classification; **CR**, Czech Republic; **CRUCIAL**, caduet vs. usual care in subject with hypertension and additional risk factors study; **CZK**, Czech crown; **DDD**, defined daily dose; **DID**, DDD per 1000 inhabitants per day; **ENHANCE**, ezetimibe and simvastatin in hypercholesterolaemia enhances atherosclerosis regression study; **JUPITER**, justification for the use of statin in primary prevention: an intervention trial, evaluating rosuvastatin; **SATURN**, study of coronary atheroma by intravascular ultrasound: effect of rosuvastatin versus atorvastatin; **SHARP**, study of heart and renal protection; **STEP**, statin therapy results in the real world practice in the Czech Republic project.

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