The mortality of patients with diabetes mellitus using oral antidiabetic drugs in the Czech Republic decreased over the decade of 2003–2013 and came closer to the population average

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Summary
Introduction: Every year official data is published which describes the care of patients with diabetes mellitus in the Czech Republic. An overall number of individuals with diabetes, the number of newly reported cases and the number of patient deaths is always specified. However this data does not allow us to identify the differences in mortality between the individual cohorts of diabetic patients in relation to therapy. **Goal:** Comparison of the mortality development in the periods of 2002–2006 and 2010–2013 in a representative sample of the patient population with type 2 diabetes mellitus using oral antidiabetic drugs, kept in the database of the General Health Insurance Company of the Czech Republic (VZP) which provided health care coverage for 63% of Czech population in 2013. **Methodology:** A retrospective epidemiologic analysis. We identified all individuals in the VZP database who had a record of DM diagnosis (E10 – E16 based on ICD 10) or who had any antidiabetic therapy prescribed (ATC group A10) in the periods of 2002–2008 and 2009–2013. We only selected those patients for the analysis who were treated with oral antidiabetic medicines (in the given year or the preceding years they had a record of treatment with at least one medicine from A10B group, while having no record of treatment with medicines from A10A group within both years). 237 665 individuals met the selected criteria in 2003 and 315 418 individuals in 2013. **Results:** Mortality rates dropped for all age groups (from 2003–2013): for 50–59 year olds by 1.2%-0.7%; in 60–69 year olds by 2.6%–1.6%; for 70–79 year olds by 5.8%-3.5%. In 2013 mortality rates came close to the general population where for the same age groups they reached 0.6%, 1.5% and 3.4% respectively. When expressed in relative terms, the mortality among 50–59 year olds declined by 42% (Czechia by 25%), among 60–69 year olds by 39% (Czechia by 17%) and among 70–79 year olds by 40% (Czechia by 28%) from the year 2003. The decline in mortality among the patients with DM treated with oral antidiabetic medicines was greater in both absolute and relative terms in the period of 2003–2013 than among the general population in the Czech Republic. **Conclusion:** The analysis of mortality among the patients treated with oral antidiabetic medicines, registered in the VZP database, has shown a clearly favourable trend of mortality decline which is faster than among the general population. The fact that mortality among this cohort is getting closer to that among the general population of the corresponding age is a finding of critical importance. There is a justified expectation that mortality, with increasingly extensive utilization of the present therapeutic procedures, will continue to decrease.

Key words: diabetes mellitus – mortality – oral antidiabetic medication

Introduction

In the Czech Republic patients with diabetes mellitus (DM) are followed and treated predominantly by specialists (approx. 80 % at a specialist diabetology clinic), a minor part by general practitioners (up to 20 %). [1].

The only relevant public source in the Czech Republic which displays information about the therapy of diabetes mellitus (DM), is the statistics of the Institute of Health Information (ÚZIS) [1]. Every year raw data is published which describes the care for patients with diabetes. An overall number of individuals with diabetes, the number of newly reported cases and the number of patient deaths are always specified. However this data does not allow us to identify the differences in mortality between the individual cohorts of diabetic patients in relation to therapy.

Since the publication of the results of the Framingham study [2] and the work by Haffner et al. [3] it has been commonly stated that the mortality of patients with type 2 DM (DM2T) is several times higher as compared with a non-diabetic population; an excessive mortality rate is primarily related to an increased cardiovascular risk. In particular during the last 15 years, however, essential changes took place concerning possibilities of impacting the cardiovascular risk (introduction of statins, a safe therapy of hypertension using the potential of drugs acting on the angiotensin-renin system, procedures of invasive cardiology). It has been proven that therapeutic goals at the level of non-diabetic population can be set for patients without serious complications [4]. Gradual implementation of the therapy for DM which demonstrably reduces cardiovascular risks would be expected to reduce the mortality rate in patients with DM. In the Czech Republic the development of the mortality rate in this group of patients has not been recently evaluated, with the exception of one publication [5]. Also the mortality rate among patients only treated with oral antidiabetic drugs is only exceptionally evaluated in the world literature.

The aim of the study

Comparison of the mortality development in the periods of 2002 – 2006 and 2010 – 2014 in a representative sample of the population of patients with type 2 diabetes mellitus using oral antidiabetic drugs registered in the General Medical Insurance Company of the Czech Republic (VZP) which provided health care coverage for 63 % of Czech population in 2014.

Methodology

We identified all individuals in the VZP database, who in the periods of 2002 – 2008 and 2009–2013 had a record of DM diagnosis (E10 – E16 based on MKN 10) [6], or who had any antidiabetic therapy prescribed (ATC group A10) [7], see tab. for details. 1. Subsequently a set of patients was extracted for analysis, who had any agent from the group A10 prescribed at least once in the given year. Data exports were prepared for two non-overlapping, however at the patient level noncontinuous periods, therefore with regard to placing a patient into the defined group based on the recorded therapy both in the given year and the previous year, it was not possible to determine the number of patients treated with an antidiabetic therapy for the first year of the second export, i.e. the year 2009, based on the defined group. Consequently, the proportion of patients who died in 2009 is interpolated in the charts according to the values for the preceding and the following years (i.e. based on the rates of patients who died in 2008 and 2010). For the purpose of analysis we selected patients treated with oral antidiabetic medicines. We defined these patients as individuals who in the given or the preceding year had a record of treatment with at least one medicine from A10B group, while they had no

Table 1. An overview of selection of a cohort for final analysis and a number of patients with a record of antidiabetic therapy (E10 – E16 according to MKN 10). The patient is always assigned into a predefined group based on a recorded therapy within the given year and / or the preceding year. The condition for a patient to be assigned into a specific group is to have a record of a given therapy in one of the two years at least.

Groups of patients with a record of antidiabetic therapy in VZP data between 2002–2013

	Patients treated with antidiabetic therapy in the given year – **recorded in the given year**		Patients treated with antidiabetic therapy in the given year – **recorded in the given and preceding years**		Patients treated with antidiabetic therapy in the given year – **recorded in the given and preceding years, who died in the given year**	
	Year	no of patients	Year	no of patients	Year	no of patients
export 1	2002	294 972				
	2003	312 048	2003	339 539	2003	18 685
	2004	318 020	2004	343 887	2004	18 514
	2005	326 606	2005	351 953	2005	18 416
	2006	333 916	2006	359 455	2006	17 843
	2007	323 741	2007	346 976	2007	17 347
	2008	327 516	2008	363 467	2008	17 742
export 2	2009	366 395	2009	-	2009	-
	2010	388 050	2010	405 863	2010	17 576
	2011	407 205	2011	425 477	2011	18 317
	2012	414 673	2012	437 734	2012	18 844
	2013	418 582	2013	440 669	2013	19 310

record of treatment with medicines from A10A group (insulin) within both years. For the sake of comparison with the mortality of the general Czech population, we divided the group based on age by decades, the data applicable for the Czech Republic was obtained from the Czech Statistical Office [8].

All the data concerning patients is identified in the original database for one person by a personal identification number. The data provided by VZP and used for analysis was blinded by coding on an anonymous identifier which however enables tracing of all prescriptions and medical practices relating to a particular person.

We used the data from regular annual reports to the Institute of Health Information and Statistics of the Czech Republic (ÚZIS) [1] for some comparisons.

Results

We got a basic idea about the development of mortality from the data published by ÚZIS (Chart 1). Distinctive decline in mortality rates has been proven for the whole group of registered patients with DM in the Czech Republic between 1985 and 2013.

The set of individuals identified in the VZP database was stratified according to the aforementioned methods. 237 665 individuals met the selected criteria in 2003 and 315 418 individuals in 2013. Summary data is given in Tab. 1 and Tab. 2. Tab. 3 summarizes mortality rates in men and women by decades. The mortality rate in men is noticeably higher in the first time-period (2008–2009) than in women. The differences decrease in the second time-period (2010–2013).

The development of mortality for the individual decades in patients with DM treated with oral antidiabetic medicines is summarized in Chart 2. In the period of 2010–2013 the values come close to the general population. When expressed in percents of the year 2003, the mortality in patients with DM treated with oral antidiabetics declined in 50–59 year-old patients by 42 % (Czechia by 25 %), in 60–69 year olds by 39 % (Czechia by 17 %) and among 70–79 year olds by 40 % (Czechia by 28 %).

Discussion

The basic outcome of our analysis is the proof of gradual decrease of the risk of death among patients treated with oral antidiabetic drugs. Mortality expressed as a percentage of deceased patients within 1 year is close to the findings in recent clinical studies that evaluated cardiovascular safety of the new antidiabetic medicines (Tab. 4) [9–15]. Patients with a limited life expectancy are not included in clinical studies, average duration of diabetes is less than 10 years, patients typically get an extensive statin therapy (77 % in the EMPA – REG OUTCOM study) [15] and a consistent therapy of hypertension. On the other hand, the condition fr entry is an increased cardiovascular risk, several ten percent are treated with insulin at the entry. However if we compare the corresponding age group among the patients treated with oral antidiabetic medicines in the Czech Republic in 2013 with mortality rates specified in these studies, the outcome for the Czech Republic is favourable (Tab. 4).

Our analysis is a retrospective epidemiological non-interventional study which has several interpretation pitfalls. We evaluate the current population of patients treated with oral antidiabetic medicines. The result certainly reflects several contradictory trends. First of all the increasing number of patients treated with hypolipidemic drugs [16], a high rate of treatment with ACE inhibitors and sartans, as well as the increasing number of patients treated with metformin and the decreasing rate of those treated with sulfonylurea [17] will have a positive impact. A false positive result might be produced in the case that an incidence of newly diagnosed patients with DM significantly increased. But the ÚZIS data does not confirm a rapid increase in the number of newly registered patients with diabetes, except for the last year within the available evaluation. Patients with diabetes tend to live longer, the tendency toward the decrease in mortality is seen in all decades.

Earlier diagnosing of diabetes can also be eliminated by means of comparison with a detailed analysis of the development of incidence of new detection of DM in Great Britain [18]. The overall incidence (number of newly diagnosed patients with DM2T) has been quite similar in the two countries in recent years. In Great Britain it amounts to 515 newly diagnosed individuals per 100 000 citizens in 2010, in the Czech Republic 649 patients with DM of all types per 100 000 inhabitants. New criteria for diagnosing diabetes mellitus (the diagnostic value of fasting blood glucose was reduced from 7.8 mmol/l to 7.0 mmol/l) were adopted in 2000. As

Chart 1. Mortality in the whole population of people with diabetes mellitus in Czech Republic (data: ÚZIS). Bearing in mind the indicative character of this data, an impressive decline in the whole population is observed. Expressed in percents of the whole number of patients included in ÚZIS.

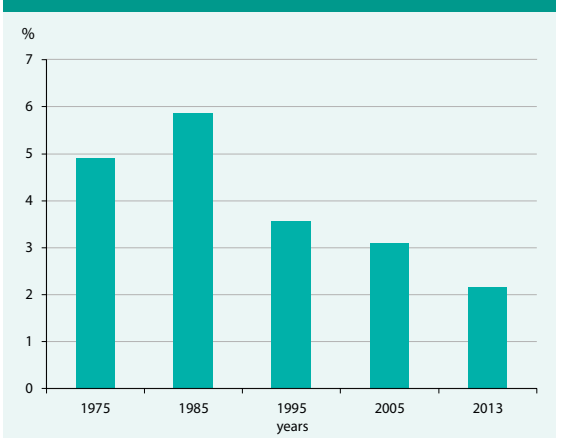


Table 2. Mortality by individual decades of patient age and comparison with mortality in Czech general population in corresponding decades (data: Czech Statistical Office)

Year	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
DM and PAD (VZP)	237 665	239 492	243 900	248 653	237 911	249 983		285 788	302 650	313 048	315 418
Deceased	11 350	11 132	10 841	10 402	10 082	10 152		9 605	10 170	10 607	10 984
%	4,8	4,6	4,4	4,2	4,2	4,1		3,4	3,4	3,4	3,5
age 50–59 Czechia	0,8	0,8	0,7	0,7	0,7	0,7	0,7	0,7	0,7	0,6	0,6
age 50–59 PAD	1,2	1,2	1,2	1,2	1,1	1,2		0,8	0,8	0,8	0,7
age 60–69 Czechia	1,8	1,7	1,7	1,6	1,5	1,5	1,5	1,5	1,5	1,5	1,5
age 60–69 DIA	2,6	2,5	2,3	2,1	2	1,9		1,5	1,6	1,6	1,6
age 70–79 Czechia	4,7	4,4	4,4	4,1	4,1	3,9	3,9	3,7	3,6	3,5	3,4
age 70–79 DIA	5,8	5,8	5,6	5,1	5,1	4,8		3,7	3,5	3,4	3,5
80 years of age and older, Czechia	13,8	12,9	12,8	12,1	11,9	11,8	12,1	11,8	11,6	11,8	11,8
80 years of age and older, DIA	14,2	14	13,6	13,3	12,7	13		10,5	10,6	10,8	11

Values specified in %.
Czechia – Czech Republic – general population **PAD** – patients treated only with oral diabetic drugs

Table 3. Comparison of mortality between men and women within individual age groups from the basic cohort defined by the methodology (the patient always assigned into a predefined group based on a recorded therapy in the given year and / or the preceding year, i.e. in order to be assigned into a specific group the patient must have a record of a given therapy in one of the two years at least)

	MEN						WOMEN					
	Mortality in a given group (% patients died)						Mortality in a given group (% patients died)					
Year	Age						Age					
	0–39 years	40–49 years	50–59 years	60–69 years	70–79 years	80+ years	0–39 years	40–49 years	50–59 years	60–69 years	70–79 years	80+ years
2003	0,2	0,8	1,5	3,3	7,2	16	0,3	0,4	0,8	1,9	4,9	136
2004	0,3	0,8	1,5	3,2	7,3	16,1	0,5	0,5	0,8	1,8	4,9	13,1
2005	0,2	0,8	1,4	2,9	6,8	15,4	0,3	0,5	0,8	1,6	4,8	12,9
2006	0,1	0,8	1,4	2,6	6,4	15	0,1	0,4	0,8	1,5	4,3	12,6
2007	0,3	0,8	1,4	2,6	6,3	13,9	0	0,5	0,8	1,4	4,3	12,2
2008	0,2	0,7	1,2	2,6	5,9	14,4	0,1	0,4	0,7	1,2	4	12,4
2009	–	–	–	–	–	–	–	–	–	–	–	–
2010	0,2	0,4	1	1,9	4,5	11,8	0,1	0,2	0,6	1,1	3,1	9,9
2011	0,3	0,5	0,8	2	4,4	11,6	0	0,3	0,7	1,2	2,8	10,1
2012	0,2	0,3	0,9	2	4,3	11,8	0,3	0,4	0,6	1,1	2,8	10,3
2013	0,4	0,5	0,9	2	4,4	12,1	0,1	0,2	0,4	1,2	2,8	10,4

shown by the charts in the commented study, a rapid increase of the newly diagnosed patients with DM occurred in recent years, which testifies to a careful active screening conducted by general practitioners in Great Britain, after 2 years of the increasing incidence from 2000 it declined and kept to the same level for several years. In the Czech Republic a similar course was not recorded, a gradual increase only started after 4 years and the incidence was sustained for another 5 years [1]. This course is consistent with the continuously increasing number of patients with DM without any variations – that indicates that general practitioners in the Czech Republic, at least in the first half of the last decade, did not conduct active screening, did not detect patients who fell within the range of borderline level fasting blood glucose. If it had been the case, they should reclassify their disorder as manifest DM within 1 year. This not having happened is an indirect confirmation of the

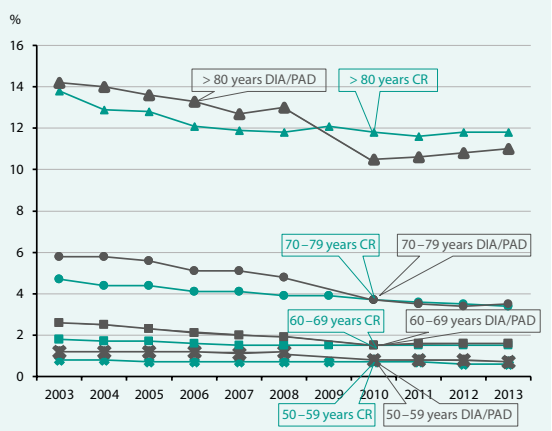
fact that DM is diagnosed later in the Czech Republic, in patients with blood glucose > 7.8 mmol/l.

Mortality also correlates, apart from other factors, with the duration of DM and age. The results of our analysis might be affected by the increasing life expectancy in the general population. Therefore more patients reach a higher age when manifestation of a genetic predisposition for DM2T is more likely. Subsequently, if they were identified right after exceeding the diagnostic blood glucose for DM, they would be treated with metformin. There is not enough data available for analysis at present to confirm or eliminate such distortion.

The preliminary results of the analysis of the VZP database – now being thoroughly reviewed and prepared for publication – testify in favour of a positive impact of the new safe therapy (gliptins) on the mortality rates. Chart 3 shows a statistically significant difference in the development of mortality between the patients who had a therapy initiated either with gliptin or any sulfonylurea. According to preliminary analyses, the overall result is affected by a difference relating to higher age groups: the risk of death increases with age in the case of sulfonylurea therapy. The groups are very similar with regard to concomitant medications with a proven impact on mortality and a number of performed cardiovascular practices. Chart 4 shows how serious risk the sulfonylurea therapy can pose to people aged 60–69 years as compared to the treatment with gliptins in patients treated with insulin. These preliminary results are in accordance with the hypothesis that the greatest danger of an intensive therapy in patients, especially those at higher age, is the risk of hypoglycemia.

Hypothetically it can be speculated about a possible reduction of mortality in patients with DM treated with oral antidiabetic drugs below the level of the general Czech population. In 2013 hypolipidemic drugs were used in the treatment of 55.6 % of all the persons registered in the VZP data [16], who had antidiabetic treatment prescribed, in < 5 % ezetimib was prescribed in a combination, while the median LDL-cholesterol level in a non-selected group of patients with diabetes tested in the Synlab company laboratories from 2010 to 2015, equalled 2.9 mmol/l (68 509 tests for 57 168 individuals for whom a test for glycated haemoglobin was indicated) [19]. If the statin therapy [20] and in particular its combination with ezetimib is fully utilized [21], a significant reduction of mortality can be expected.

Chart 2 Mortality by age groups



Axis x – year

Axis y – mortality expressed in percents of the general population in the given year

Czech Republic – the whole Czech population **DIA/PAD** – patients with diabetes treated with oral antidiabetic drugs

Conclusion

There were only those treated with oral antidiabetic drugs selected from the cohort of patients identified in the VZP database. 237 665 individuals met the selected criteria in 2003 and 315 418 individuals in 2013.

The analysis of mortality among the patients in the VZP database treated with oral antidiabetic medicines, has shown a clearly favourable trend of its decline. The finding that mortality among this cohort is getting closer to that among the general population is of critical importance. It can also be expected that with an increasingly extensive utilization of the present therapeutic procedures, mortality will continue to decrease.

The result of the analysis is in agreement with the tendency of decline in the serious complications of diabetes (amputation) [22], and improvement in the use

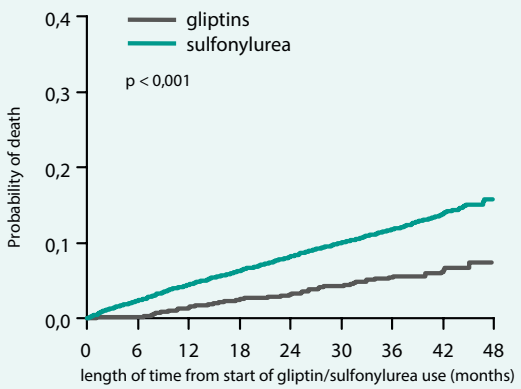
Table 4. Mortality in clinical studies. Modified acc. to [23–29]

	ACCORD	VADT	ADVANCE	ORIGIN	TECOS	SAVOR – TIMI 53	EMPA -REG	ČR/DIA/PAD (2013)
Intensive therapy	1,14	2,04	1,78	2,57	2,48	2,9	1,94	1,6
Standard therapy	1,14	1,89	1,92	2,6	2,45	2,5	2,86	
Average age (years)	62	60	66	60	65,5	65	63	60–69

Mortality is expressed in percents/per100 patient years. The study differs by initial therapies, but the large majority of probands are diabetic patients treated with oral antidiabetic drugs with an increased risk of cardiovascular complications, or such complication is already in their anamnesis.

Czechia/DIA/PAD – mortality in comparable population of patients treated in Czech Republic with oral antidiabetic drugs (database VZP)

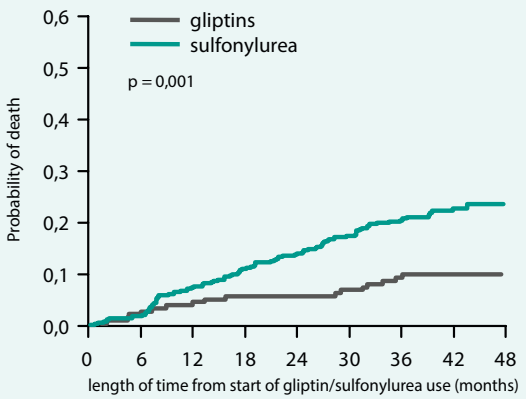
Chart 3. Probability of death in patients with DM treated with gliptins or sulfonylurea – treated with PAD only, all age categories



length of time from start of treatment	probability of death (%, 95% IS)	
	gliptins (n = 1365)	sulfonylurea (n = 7632)
6 months	0.22 (0.07–0.68)	2,39 (2.07–2.76)
12 months	1.33 (0.84–2.10)	4,47 (4.03–4.96)
24 months	3.21 (2.39–4.30)	8.19 (7.60–8.83)
36 months	5,44 (4.34–6.80)	11.83 (11.12–12.59)

The difference between the development of probability of death regarding individuals who had a gliptin therapy initiated, as opposed to those initially treated with any sulfonylurea. The patient was included in the evaluation based on a therapy record in 2009 and 2010. In both years they had to be only treated with PAD, while the treatment with gliptins/sulfonylurea was not started until the year 2010. The overall result is influenced, according to preliminary analyses, by the difference within higher age groups. The groups are very similar with regard to concomitant medications with a proven impact on mortality and a number of performed cardiovascular practices. In all patients treated with oral antidiatetics in the period of 2009–2010 whose treatment with gliptins/ sulfonylurea was initiated in 2010, a statistically relevant difference in probability of dying was proven between the patients treated with gliptins on the ne hand, and those treated with sulfonylurea on the other. The patients treated with sulfonylurea face a higher probability of death than the patients treated with gliptins. However the groups of patients distinguished by the medicines administered are not comparable in terms of age (preliminary results).

Chart 4. Probability of death in patients with DM treated with gliptins or sulfonylurea – treated with insulin, category of 60–69



length of time from start of treatment	probability of death (%, 95% IS)	
	gliptins (n = 173)	sulfonylurea (n = 397)
6 months	2.32 (0.88–6.06)	2.02 (1.01–3.99)
12 months	4.64 (2.35–9.07)	7.57 (5.36–10.65)
24 months	5.82 (3.18–10.55)	13.90 (10.86–17.72)
36 months	9.42 (5.88–14.92)	20.57 (16.90–24.91)

The patient was included in the evaluation based on a therapy record in 2009 and 2010. In both years the patient had to be treated with insulin, while a gliptin/sulfonylurea therapy was not started until the year 2010. For patients aged from 60–69 years treated with insulin from 2009 to 2010 a statistically relevant difference was proven in the estimates of probability of death based on the application of gliptins or sulfonylurea. A significantly lower mortality was observed in the patients treated with gliptins as compared to those treated with sulfonylurea (as per preliminary results).

of statins [16] and metformin [17] in treatment. This testifies to the improving quality of the care for patients with DM in the Czech Republic.

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