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COMMENTARY

Results of Insulin Therapy in Type 2 Diabetes Mellitus Patients in the Czech Republic: Do They Reflect the Current Status in Other Countries?

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ABSTRACT

The results of two large multicentric, observational and cross-sectional studies (the DIAINFORM study and BALI study) reflecting routine clinical practice for insulin treatment in type 2 diabetes mellitus in the Czech Republic were published recently. In this commentary, we analyze these results and compare them with the findings of similar studies conducted in other countries within the last decade. The analysis focuses on achievement of glycated hemoglobin goals, insulin dosage and frequency of hypoglycemia.

Keywords: Basal insulin initiation; HbA1c; Hypoglycemia; Insulin titration; Metabolic control; Type 2 diabetes

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INTRODUCTION

We have recently published the results of two large studies (the DIAINFORM study and BALI study) reflecting the routine clinical practice for insulin treatment of persons with type 2 diabetes mellitus (T2DM) in the Czech Republic [1, 2]. In the DIAINFORM study, there was an additional representative sample of patients from the Slovak Republic. Both studies were multicentric, observational and cross-sectional in design and were aimed to convey "the whole country therapy picture" regarding the achievement of glycated hemoglobin (HbA1c) treatment goals (DIAINFORM study) and basal insulin initiation (BALI study). Although the sets of physicians and patients used were somewhat limited in terms of diversity, the studies do provide a more complex picture of the results of this type of treatment than is usually available. We have analyzed the results of these two studies and attempted to compare them with the results from studies conducted in other countries which, in our opinion, have a similar design and representativeness and were published in this decade (Table 1).

Compliance with Ethics Guidelines

This article is based on previously conducted studies, and all study procedures in these studies were carried out in accordance with the

Table 1 Results of multicentric or large registry-based studies focused on the achievement of glycated hemoglobin targets

Country, year of publication	Number of patients	Therapy[a]				
		Diet/exercise	1 OAD	2 OADs	3+ OADs	Insulin
Czech Republic, 2018 [1]	702	–	–	–	–	35.7
Slovak Republic, 2018 [1]	332	–	–	–	–	28.3
China, 2017 [5]	2454	78.1	61.8	49.8	42.4	26.8
USA, 2016 [3]	4947	–	–	–	–	31.4[b]
EU, 2012 [4]	5811	87.9	76.1	61.4	49.9	36.1[c]

Only studies published within this decade are included. Data on patients not treated with insulin are also presented if collected in a study

HbA1c Glycated hemoglobin, *OADs* oral antidiabetic drugs

[a] Data are presented as the percentage (%) of patients who achieved a HbA1c level of < 7% on the respective therapeutic regimen. Patients on OADs are categorized as taking one OAD (1 OAD), two OADs (2 OADs) and three or more OADs (3+ OADs), respectively

[b] Patients with all types of diabetes were included in the study

[c] Patients treated with injectables (insulin and glucagon-like peptide-1 analogs) were included in this group

International Conference on Harmonization/ Good Clinical Practice. The final study protocol was approved by the Ethics Committee of the National Institute of Endocrinology and Diabetology in Lubochna, Slovak Republic (approval date 4 Feb 2015). All participants provided written informed consent.
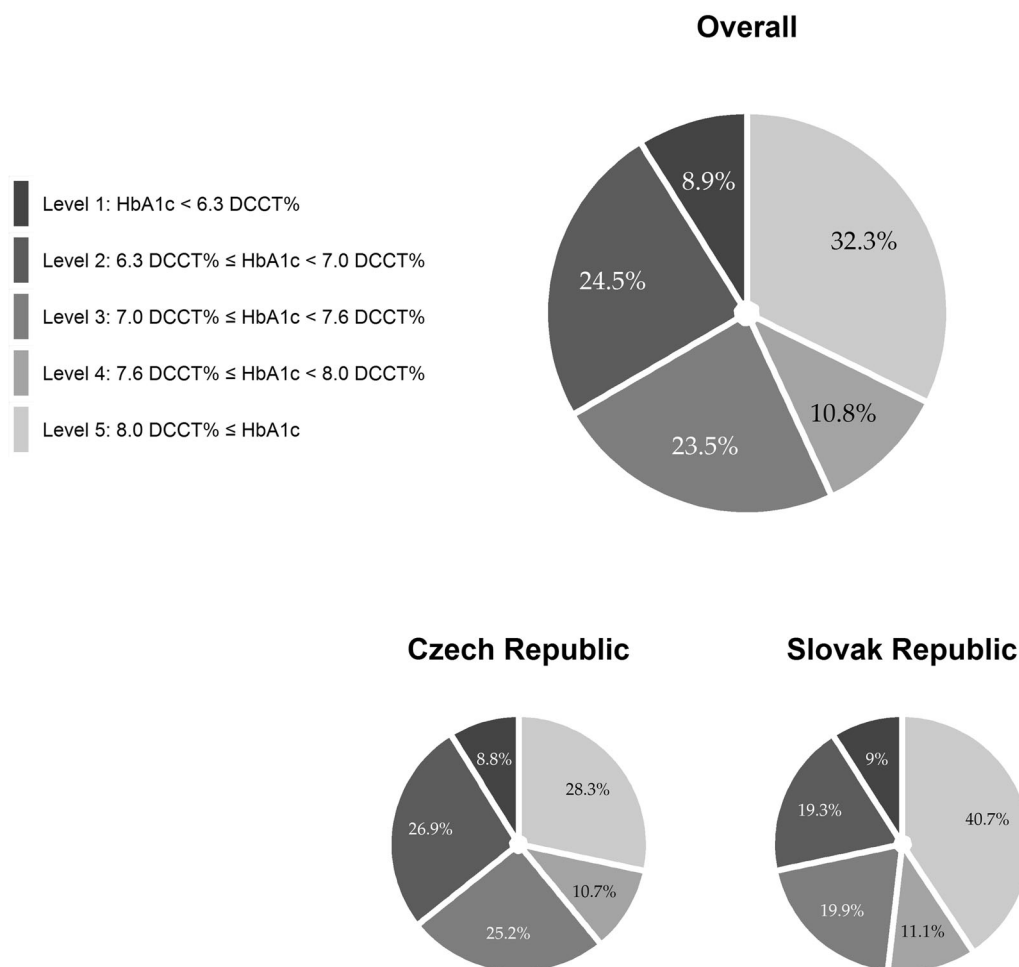
TREATMENT TARGETS ACHIEVEMENT STUDIES

HbA1c Levels

The DIAINFORM study was conducted in routine clinical practice settings at 141 centers in the Czech and Slovak Republics [1]. Data were analyzed from a total of 1034 patients with T2DM, proportionally corresponding to the number of patients in both countries and also to the types of treatment: (1) basal insulin and oral antidiabetic drugs (OADs), (2) premixed insulin and (3) multiple daily insulin doses (MDI). The primary objective of the study was to determine the percentage of patients with HbA1c target values of < 7% (53 mmol/mol). The DIAINFORM study showed that only 35.7 and 28.3% of patients in the Czech Republic and Slovak Republic, respectively, achieved this

target HbA1c value. Within the whole study population (Czech Republic and Slovak Republic together) the target HbA1c of < 7% was reached by 33.4% of patients (Fig. 1).

Of the patients with T2DM treated with two doses of premixed insulin, 31% achieved HbA1c target values of < 7% (53 mmol/mol); in comparison, 35.9 and 31.9% of patients treated with basal insulin and OADs, and with MDI, respectively, achieved the HbA1c target values of < 7% (53 mmol/mol).

Very similar results were obtained in a registry-based study in the USA [3] and in the PANORAMA study conducted in the EU and Turkey [4]. The proportion of the population with HbA1c < 7% in each country in the latter study was not reported, but we can presume that it varied as the proportion of patients in the whole study population (T2DM patients receiving different types of therapy were involved) achieving the HbA1c target ranged from 74.1% in The Netherlands to 63.7% in Germany and 48.0% in Turkey [4]. Unfortunately for comparison purposes, patients with all diabetes types were included in the analysis in the US study, and in the PANORAMA study patients treated with insulin but also with glucagon-like peptide-1 analogs were analyzed together. Thus, neither of these studies show

Overall

Level 1: HbA1c < 6.3 DCCT%

Level 2: 6.3 DCCT% ≤ HbA1c < 7.0 DCCT%

Level 3: 7.0 DCCT% ≤ HbA1c < 7.6 DCCT%

Level 4: 7.6 DCCT% ≤ HbA1c < 8.0 DCCT%

Level 5: 8.0 DCCT% ≤ HbA1c

Czech Republic

Slovak Republic

Fig. 1 The proportion of patients categorized according to glycated hemoglobin (*HbA1c*) values for the whole study population and separately for the Czech Republic and Slovak Republic [1]. *DCCT* Diabetes Control and Complications Trial

results that focus only on T2DM patients treated with insulin. In addition, the results from different insulin regimens were not reported in either study.

To our knowledge, the only study in Asia that has focused on achievement of HbA1c targets and insulin dosage was a cross-sectional study in China which revealed that 26.8% of the insulin-treated patients achieved HbA1c values of < 7% [5].

Regarding the weaknesses of the above-mentioned studies, we may conclude that the proportion of T2DM patients treated with insulin who achieved the HbA1c target values

of < 7% varies around 30% in all of these studies.

It should be noted that in terms of reflecting real-life clinical practice, none of these studies (including the DIAINFORM study) incorporate individualized HbA1c targets. The inclusion of this parameter could change the perspective of the HbA1c results substantially. In the DUNE study [6], individualized HbA1c targets were set up by patients' physicians or the study experts according to international guidelines [7] into several groups: < 7% for 18% of patients, 7.0 to < 7.5% for 57%, 7.5 to < 8.0% for 17% and ≥ 8.0% for 6.8% of patients.

If we virtually apply this model of individualized HbA1c targets to the DIAINFORM study (which had a study population with an even higher mean age, weight, body mass index and diabetes duration than the others), we could speculate that in terms of achieving target HbA1c values of < 7% the results may be better than they appear (Fig. 1), as some of the patients with a HbA1c value of ≥ 7.0% may actually have achieved their personal goals. However, even with individualized HbA1c targets taken into consideration, we can be sure that a substantial number of patients did not reach their individual target, with many of these having a HbA1c value of ≥ 8% (28.4% of study population).

The achievement of individualized HbA1c targets and thus of better HbA1c target results may also be true for the other studies mentioned above, but fine stratification of the HbA1c results was not performed in any of these studies.

Insulin Doses

In the DIAINFORM study, in contrast to the other studies mentioned above, we obtained and analyzed values of insulin doses. The mean insulin dose in the group of patients receiving combination therapy of basal insulin and OAD(s) was 0.28 IU/kg per day; in comparison, in those treated with premixed insulin and in those treated with MDI it was 0.50 and 0.65 IU/kg per day, respectively. These doses are lower than those usually see in randomized clinical studies (RCS) [8–10], possibly because, unlike in clinical studies, a relatively higher number of patients in the DIAINFORM study did not reach the recommended HbA1c values. This difference reflects the actual possibilities of real clinical practice as opposed to clinical studies during which the usual patient care is extended by a precise protocol, improved education, a sufficient number of test strips, telephone consultations, among other supportive measures. Of course, the fear of hypoglycemia, by both the patient and the physician, may also play a role in increasing the dose [11]. A recently published multicentric observational study in patients treated with insulin conducted in Central and Eastern European countries, including the Czech Republic, showed that the fear of hypoglycemia is also common among T2DM patients. Most type 1 diabetes and T2DM patients rated their fear level as 5 on the 10-point scale (where 10 indicates 'absolutely terrified'). Separate data for the Czech Republic were not presented in that study [12].

Frequency of Hypoglycemia

None of the studies mentioned, including the DIAINFORM study, presented the frequency of hypoglycemia among the study groups.

BASAL INSULIN INITIATION STUDIES

HbA1c Levels

The BALI study was a prospective observational study conducted in routine clinical practice settings at 137 centers in the Czech Republic [2]. It described the practices associated with the initiation of basal insulin therapy in T2DM patients whose condition was insufficiently controlled during treatment with OADs. Among these patients, only 18% reached the HbA1c target value of < 7% after 6 months of insulin treatment; in comparison to the baseline HbA1c levels, the mean HbA1c values of the patients dropped from 9.2 to 8.2 after 3 months of insulin treatment and to 7.9% after 6 months (Table 2). The study showed the highest decrease in HbA1c in the group of patients whose baseline HbA1c value was > 9% (− 2.4%), while the lowest drop was in those with a mean baseline HbA1c value of < 8% (− 0.43%). The mean fasting blood glucose decreased from 11.3 to 8.4 mmol/l after 3 months of insulin treatment and to 8.0 mmol/l after 6 months. Both mean HbA1c and fasting glucose values show that patients experienced major improvement in HbA1c within the first 3 months of initiating insulin treatment, while during the subsequent 3-month period the decrease was much smaller.

Table 2 Results of studies focused on the initiation of insulin treatment

Country, year of publication	Number of patients	Percentage of patients with HbA1c < 7% at baseline	Percentage of patients with HbA1c < 7% after 3 months of insulin treatment	Percentage of patients with HbA1c < 7% after 6 months of insulin treatment	Percentage of patients with HbA1c < 7% after 2 years	Mean HbA1c at baseline (%)	Mean HbA1c at after 3 months of insulin treatment (%)	Mean HbA1c after 6 months of insulin treatment (%)	Percentage of patients experiencing hypoglycemia, all events (severe events)	Mean insulin dose after 6 months of insulin treatment (U/day, U/kg per day)
Czech Republic, 2019 [2]	1426	0	–	18.0	–	9.2	8.2	7.9	12.3 (0.1)	18.8 ± 8.9, 0.21 ± 0.1
USA, 2018 [13]	5679	–	–	21.5	–	9.1	–	7.6	–	–
France, 2017 [14]	2264	12.7	19.6	–	27.6	9.0	–	–	–	–
Germany, 2017 [14]	2330	18.1	28.0	–	33.4	8.5	–	–	–	–
Italy, 2017 [14]	1228	12.5	20.0	–	27.4	9.1	–	–	–	–
Spain, 2017 [14]	1117	10.6	20.4	–	23.9	9.2	–	–	–	–
UK, 2017 [14]	3468	4.4	8.1	–	17.3	9.9	–	–	–	–
USA, 2017 [14]	30,220	14.5	21.6	–	28.8	8.9	–	–	–	–
Taiwan [15]	836	–	6.9	10.7	–	10.1	8.9	8.7	11.4 (0.7)[a]	17.7 ± 10.0, –

[a] During 24 weeks of the study

Interestingly, the mean HbA1c after 6 months of insulin treatment is very similar to that found in the DIAINFORM study, with a difference of only 0.2% in the whole study group of patients with a mean duration of diabetes of 5.8 years. Although we are aware of non-identical sets of patients in both highly representative studies, such a small difference in mean HbA1c values suggests that in general there might be a very limited additional improvement in HbA1c values after the first 6 months of insulin treatment.

A comparison of the BALI study results with those of studies performed in other countries showed very similar results (Table 2). In a retrospective study conducted in the USA with a cohort representative of patients with T2D who initiated basal insulin from their current regimen of OAD(s), 21.5% of patients achieved HbA1c < 7% after 6 months of basal insulin treatment [13]. The mean HbA1c decreased from 9.1 to 7.6% after the first 6 months with no further improvement during the next 18 months. Cumulatively, about 38% of patients reached the HbA1c target value of < 7% in the first year; only approximately 8% more did so in the second year [13]. This finding also supports our former suggestion about there being only a small improvement in HbA1c after the first 6 months of basal insulin treatment.

Another retrospective multinational study focused on the achievement of the HbA1c target of < 7% showed that the percentage of patients achieving this goal varied among countries, from 8.1 to 28.0% at 3 months after the first prescription of basal insulin, and from 17.3 to 33.4% at 24 months [14]. In a Taiwanese study, 6.9% of patients reached the HbA1 target at 3 months and 10.7% at 24 weeks after basal insulin initiation [15].

We can conclude from these results that the HbA1c levels achieved by the patients participating in all of the studies mentioned are very similar, with the proportion of patients achieving the HbA1c target not exceeding one-third of the studied populations even in the long term follow-up.

An important fact we noted is that the mean baseline HbA1c value in all of the study populations was quite high and varied from 8.5 to 10.1%, suggesting a significantly delayed start of insulin therapy in these patients.

Insulin Doses

The mean daily basal insulin dose in the BALI study at baseline, 3 months post initiation of insulin therapy and 6 months post initiation of insulin therapy was 11.9 ± 5.19 U (0.13 U/kg per day), 16.4 ± 7.99 U (0.18 U/kg per day) and 18.8 ± 8.9 U (0.21 U/kg per day), respectively [2]. The mean daily basal insulin dose in the above-mentioned Taiwanese study reached similar values, but the authors did not report the mean daily dose per kilogram body weight [15]. Mean insulin doses in both of these studies suggest that physicians start at levels which are very close to the lower limit of recommended values [7]. The dose increase between the third and sixth month is small in the DIAINFORM study and even smaller between the third and 24th month in the Taiwanese study. These results, especially those of the Taiwanese study, strongly suggest insufficient insulin titration.

Insulin dose levels were not reported by the authors of the other studies discussed here.

Frequency of Hypoglycemia

In the BALI study 12.3% of patients experienced hypoglycemia during the study, while only one patient experienced a severe hypoglycemic event [1]. In the multinational study mentioned above [14], the authors reported that during the first year of their study 5.1% of patients experienced a hypoglycemic event; this increased to 8.9% of patients after 24 months. The frequency of severe hypoglycemia was not separately reported. In the Taiwanese study [15], 11.4% of patients were reported to have experienced hypoglycemia. A decrease in incidence was noted between week 12 and week 24, with a drop from 8.6 to 5.2% [15]. Six patients experienced severe hypoglycemic events. None of the other mentioned studies presented the frequency of hypoglycemia among the study groups.

The rate of overall hypoglycemia, including severe hypoglycemic events, in these studies,

was substantially lower than that usually reported in RCS [16, 17]. This difference is most likely linked to a smaller decrease in HbA1c than is usually experienced in RCS.

CONCLUSION

Based on the results represented here we conclude that the results of the insulin therapy in T2DM patients in the Czech Republic partly replicate those obtained in other countries. One of the main reasons for not achieving the HbA1c target in a substantial proportion of patients seems to be low doses of insulin. Fear of hypoglycemia may also play a role, but the titration studies show a rather low frequency of hypoglycemia. It is important to note that in all of the studies mentioned here that focused on insulin initiation, the mean HbA1c level at baseline was quite high, strongly suggesting the late start of insulin therapy in these patients. The results support a more active treatment approach.

Our recommendations for future real-life studies focused on insulin in the therapy of T2DMs patients would be to involve a personal HbA1c target which would allow a more accurate treatment target achievement analysis.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies. In these previously conducted studies, all study procedures were carried out in accordance with the International Conference on Harmonisation/Good Clinical Practice and the final study protocol was approved by the Ethics Committee of the National Institute of Endocrinology and Diabetology in Lubochna, Slovak Republic (approval date 4 Feb 2015). All participants provided written informed consent.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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