

# Flexible Intensive Insulin Therapy in Adults With Type 1 Diabetes and High Risk for Severe Hypoglycemia and Diabetic Ketoacidosis

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**OBJECTIVE**— Diabetes treatment and teaching programs (DTTPs) for type 1 diabetes, which teach flexible intensive insulin therapy to enable dietary freedom, have proven to be safe and effective in routine care. This study evaluates DTTP outcomes in patients at high risk for severe hypoglycemia and severe ketoacidosis.

**RESEARCH DESIGN AND METHODS**— There were 96 diabetes centers that participated between 1992 and 2004. A total of 9,583 routine-care patients with type 1 diabetes were examined before and 1 year after a DTTP. History of repeated severe hypoglycemia/severe ketoacidosis was an indication for DTTP participation. Before-after analyses were performed for subgroups of patients with three or more episodes of severe hypoglycemia or two or more episodes of severe ketoacidosis during the year before a DTTP. Main outcome measures were GHb, severe hypoglycemia, severe ketoacidosis, and hospitalization.

**RESULTS**— A total of 341 participants had three or more episodes of severe hypoglycemia the year before a DTTP. Mean baseline GHb was 7.4 vs. 7.2% after the DTTP, incidence of severe hypoglycemia was 6.1 vs. 1.4 events · patient<sup>-1</sup> · year<sup>-1</sup>, and hospitalization was 8.6 vs. 3.9 days · patient<sup>-1</sup> · year<sup>-1</sup>. In mixed-effects models taking effects of centers and diabetes duration into account, mean difference was -0.3% (95% CI -0.5 to -0.1%;  $P = 0.0006$ ) for GHb and -4.7 events · patient<sup>-1</sup> · year<sup>-1</sup> (-5.4 to -4;  $P < 0.0001$ ) for severe hypoglycemia. A total of 95 patients had two or more episodes of severe ketoacidosis. GHb was 9.4% at baseline versus 8.7% after DTTP; incidence of severe ketoacidosis was 3.3 vs. 0.6 events · patient<sup>-1</sup> · year<sup>-1</sup>, and hospitalization was 19.4 vs. 10.2 days · patient<sup>-1</sup> · year<sup>-1</sup>. In linear models with diabetes duration as the fixed effect, the adjusted mean difference was -2.7 events · patient<sup>-1</sup> · year<sup>-1</sup> (95% CI -3.3 to -2.1;  $P < 0.0001$ ) for severe ketoacidosis and -8.1 days (-12.9 to -3.2;  $P = 0.0014$ ) for hospitalization.

**CONCLUSIONS**— Patients at high risk for severe hypoglycemia or severe ketoacidosis may benefit from participation in a standard DTTP for intensive insulin therapy and dietary freedom.

*Diabetes Care* 29:2196–2199, 2006

**S**trict glycemic control reduces microvascular complications in type 1 diabetes (1). For a long time now, the inverse relation between intensive insulin therapy and high risk for severe hypoglycemia was accepted to be inevitable and has limited the use of intensive insulin therapy in routine care (2). This para-

digms changes because there is increasing evidence that structured self-management programs for intensive insulin therapy can improve glycemic control toward near normoglycemia without increasing the risk of severe hypoglycemia (3–5).

Recently, we published results of a prospective implementation study (6) with >9,500 patients who participated in a standard training program for flexible intensive insulin in type 1 diabetes to enable dietary freedom (diabetes treatment and teaching program [DTTP]). The DTTP was effective and safe in routine care. Glycemic control was improved without increasing the risk of severe hypoglycemia. The program was first introduced in 1978 (7). It consists of a 5-day structured inpatient training course for intensive insulin therapy. Patients are taught to match insulin doses to their food choices, while keeping blood glucose close to normal. The effectiveness of the DTTP was evaluated in several controlled clinical trials (4,7–9).

The DTTP has become the standard treatment approach for individuals with type 1 diabetes in Germany and Austria (10–12). However, concern has been raised about the safety and effectiveness of the DTTP in people who have problems with hypoglycemia. Although patients with a high risk for severe hypoglycemia or severe ketoacidosis are not excluded from the standard DTTP, effects might be different in these individuals.

The present article reports the results of subgroup analyses of participants with a history of repeated severe hypoglycemia or severe ketoacidosis. Although the program was not specifically designed to target the special requirements of these patient subgroups, we hypothesized that these patients would also benefit from the standard DTTP.

## RESEARCH DESIGN AND METHODS

### The DTTP

Detailed descriptions of the DTTP have been published (7,12,13). In short, the

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Received for publication 5 April 2006 and accepted in revised form 7 June 2006.

U.A.M. has received advisory compensation from Roche, Germany, and Deutsche BKK and grant/research support from Roche, Germany, and LifeScan, Germany.

**Abbreviations:** DTTP, diabetes treatment and teaching program.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

DOI: 10.2337/dc06-0751

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standard DTTP is carried out as a 5-day inpatient course of 20 h. Objectives are to enable participants to improve glycemic control, to decrease the risk of hypoglycemia, and to enable dietary and lifestyle freedom. Patients are advised to measure blood glucose before main meals and at bedtime and to adjust insulin to actual blood glucose levels and their desired carbohydrate intake on a meal-by-meal basis. Standard insulin therapy consists of multiple injection therapy with NPH insulin in the morning and at bedtime and regular insulin before main meals. The DTTP courses are conducted by specially trained nurse educators and dietitians based on a written curriculum, including explicit learning objectives in a group setting with up to 10 patients.

Patients are referred by their family physicians or diabetologists. A history of repeated or unexplained severe hypoglycemia or hypoglycemia unawareness or a history of repeated ketoacidosis are indications for participation in the DTTP rather than exclusion criteria. Although the DTTP does not explicitly target these aspects, individual patient problems are addressed during the DTTP by the members of the teaching and treatment team (physicians and educators). After discharge, patients are primarily followed-up by their family physicians.

### The continuous quality assurance project

Long-term implementation of the DTTP on a national basis and quality assessment has been accomplished by the creation of a working group of hospital-based diabetes centers dedicated to this approach. This voluntary and nonprofit organization accredits diabetes clinics that undergo periodic evaluations of structure, process, and outcome quality of their programs (14). This includes a reexamination of a sample of consecutively referred patients 1 year after participation in the DTTP.

### Participants and outcome measures

Subgroups consisting of patients with three or more episodes of severe hypoglycemia or two or more episodes of severe ketoacidosis in a 12-month period before intervention were analyzed. Main outcome measures were GHb, incidence of severe hypoglycemia or severe ketoacidosis, and days spent in the hospital for any reason.

Data were recorded between 1992 and 2004 in 96 hospital diabetes clinics

all over Germany (83 general hospitals with 8,100 patients and 13 university hospitals with 1,483 patients). For evaluation of outcome quality, every center was asked to reexamine 50 consecutive patients (30 patients since 2002) 1 year after participation in the DTTP (evaluation sample). This must be repeated every 3 years. Drop-out rates should not exceed 10%.

Immediately before participation in the DTTP, and again after 1 year, the following outcome measures are assessed: 1) GHb levels are analyzed at the local hospital laboratories by using high-performance liquid chromatography. Local GHb values are adjusted to Diabetes Control and Complications Trial standards by an evaluated standardization procedure (14) using local reference ranges. 2) Episodes of severe hypoglycemia and severe ketoacidosis are assessed by interview for the preceding year. Severe hypoglycemia is defined as a condition of hypoglycemia treated by intravenous glucose or glucagon injection (14). Severe ketoacidosis is defined as a condition of diabetic ketoacidosis requiring hospital admission. Diabetic ketoacidosis was diagnosed by urinary ketone test, capillary blood gas analyses, and clinical evaluation. The individual decision regarding hospital admission was made by local hospital physicians depending on results of laboratory tests and clinical evaluation.

### Analyses

For descriptive statistical analysis, means, SDs, and absolute and relative frequencies were calculated. For the subgroup of patients with three or more episodes of severe hypoglycemia ( $n = 341$ ), mixed-effects models were used, with center as random effect and diabetes duration as fixed effect. For the subgroup of patients with two or more episodes of severe ketoacidosis ( $n = 95$ ), application of mixed models was not feasible because of the reduced sample size. Thus, linear models were applied with diabetes duration as fixed effect. Sex-specific analyses were not performed since data on sex were not recorded. A  $P$  value  $<0.05$  was considered to be statistically significant. Because of the descriptive character of this study, adjustment for multiple comparisons was not undertaken. For computations, SPSS 10.0 (SPSS, Chicago, IL) and SAS 9.13 (SAS Institute, Cary, NC) were used.

**RESULTS**— Results of analyses of the total group of 9,583 participants have been published (6). In summary, between 1993 and 2004, 96 diabetes centers provided data of 190 evaluation samples including a total of 9,583 participants: the mean ( $\pm$ SD) age at enrollment was  $38 \pm 14$  years, duration of diabetes  $13.4 \pm 10.9$  years, and GHb  $8.1 \pm 2.0\%$  at baseline and  $7.3 \pm 1.5\%$  at follow-up. For the year before the DTTP, 15% of patients reported at least one severe hypoglycemic episode (incidence  $0.37$  events  $\cdot$  patient $^{-1}$   $\cdot$  year $^{-1}$ ), whereas during the year after the DTTP, 7.7% had at least one severe hypoglycemic episode (incidence  $0.14$  events  $\cdot$  patient $^{-1}$   $\cdot$  year $^{-1}$ ). The incidence of severe ketoacidosis was  $0.09$  vs.  $0.04$  events  $\cdot$  patient $^{-1}$   $\cdot$  year $^{-1}$ , and days spent in the hospital for any reason were  $5.8$  vs.  $3.6$  days  $\cdot$  patient $^{-1}$   $\cdot$  year $^{-1}$ . In mixed-effects models, taking effects of centers, age, and duration of diabetes into account, the mean difference between follow-up and intervention was  $-0.7\%$  (95% CI  $-0.9$  to  $-0.6$ ;  $P < 0.0001$ ) for GHb and  $-0.21$  events  $\cdot$  patient $^{-1}$   $\cdot$  year $^{-1}$  ( $-0.32$  to  $-0.11$ ;  $P = 0.0001$ ) for the incidence of severe hypoglycemia.

There were 341 participants with three or more episodes of severe hypoglycemia per year. Age at enrollment was  $38 \pm 13$  years and duration of diabetes  $18.7 \pm 11.1$  years. GHb was  $7.4 \pm 1.9\%$  at baseline and  $7.2 \pm 1.5\%$  at follow-up (Table 1). The mean incidence of severe hypoglycemia was  $6.1 \pm 9.6$  events  $\cdot$  patient $^{-1}$   $\cdot$  year $^{-1}$  before intervention versus  $1.4 \pm 5.4$  events  $\cdot$  patient $^{-1}$   $\cdot$  year $^{-1}$  after intervention. The year before the DTTP, all participants of this subgroup had at least 3, 26% had  $\geq 6$ , and 8% had  $\geq 10$  episodes of severe hypoglycemia. After the DTTP, 56% of patients had none, 20% had one, 9% had two, and 15% had three or more episodes of severe hypoglycemia. The number of days spent in hospital decreased from  $8.6 \pm 15.4$  to  $3.9 \pm 10.7$  days  $\cdot$  patient $^{-1}$   $\cdot$  year $^{-1}$ . In mixed-effects models, the adjusted mean difference of severe hypoglycemia between follow-up and intervention was  $-4.7$  events  $\cdot$  patient $^{-1}$   $\cdot$  year $^{-1}$  (95% CI  $-5.4$  to  $-4.0$ ;  $P < 0.0001$ ), and adjusted mean difference of GHb was  $-0.32\%$  ( $-0.50$  to  $-0.14$ ;  $P = 0.0006$ ).

There were 95 patients who had two or more episodes of severe ketoacidosis (age at enrollment  $31.5 \pm 13$  years, duration of diabetes  $12.3 \pm 10$  years). GHb was  $9.4 \pm 2.5\%$  at baseline and  $8.7 \pm 2.5\%$  at follow-up (Table 2). The mean

**Table 1—Baseline and follow-up data of patients with two or less episodes versus three or more episodes of severe hypoglycemia during the year before the DTTP**

	Severe hypoglycemic episodes during the year before the DTTP	
	Two or less events · patient <sup>-1</sup> · year <sup>-1</sup>	Three or more events · patient <sup>-1</sup> · year <sup>-1</sup>
Patients (n)	9,242	341
Age at enrollment (years)	38.1 ± 14	38.4 ± 13.2
Duration of diabetes (years)	13.2 ± 10.9	18.7 ± 11.1
GHb at baseline (%)	8.1 ± 2	7.4 ± 1.9
GHb at follow-up (%)	7.3 ± 1.6	7.2 ± 1.5
Severe hypoglycemia at baseline (events · patient <sup>-1</sup> · year <sup>-1</sup> )	0.16 ± 0.5	6.1 ± 9.6
Severe hypoglycemia at follow-up (events · patient <sup>-1</sup> · year <sup>-1</sup> )	0.1 ± 0.6	1.4 ± 5.4
HD at baseline (days · patient <sup>-1</sup> · year <sup>-1</sup> )	5.7 ± 13.2	8.6 ± 15.4
HD at follow-up (days · patient <sup>-1</sup> · year <sup>-1</sup> )	3.6 ± 13.2	3.9 ± 10.7

Data are means ± SD. HD, hospital days.

incidence of severe ketoacidosis was 3.3 ± 2.4 events · patient<sup>-1</sup> · year<sup>-1</sup> before intervention versus 0.6 ± 1.6 events · patient<sup>-1</sup> · year<sup>-1</sup> after intervention. The year before intervention, 58% of participants had two, 21% had three, 4% had four, and 17% had five or more episodes of severe ketoacidosis per year. After the DTTP, 72% of participants had none, 15% had one, 9% had two, and 4% had three or more episodes of severe ketoacidosis. The number of days spent in hospital decreased from 19.4 ± 23 to 10.2 ± 22.6 days · patient<sup>-1</sup> · year<sup>-1</sup>. In linear fixed-effects models, the adjusted mean difference between follow-up and intervention was -2.7 (95% CI -3.3 to -2.1; *P* < 0.0001) for severe ketoacidosis and -8.1 (-12.9 to -3.2; *P* = 0.0014) for days spent in the hospital.

**CONCLUSIONS**— In the main study, ~1 of 6 patients had at least one episode of severe hypoglycemia, and <1 of 10 had one episode of severe ketoacidosis during the year before the DTTP. During the year after participation in the DTTP, these figures were more than halved (6). The present study of subgroup analyses in high-risk patients shows that these patients also have lower event rates after the DTTP. Therefore, the standard DTTP for intensive insulin therapy may reduce the risk of acute complications both in individuals with average risk and high risk for severe hypoglycemia or severe ketoacidosis without worsening metabolic control. Consequently, intensified insulin therapy and dietary freedom may be introduced even in patients with high

risk for severe hypoglycemia or severe ketoacidosis.

Likely explanations for the observed effects are that the DTTP improves self-management skills. Patients increase their competence to define individual treatment goals and to balance favorable GHb levels and an unacceptable risk of severe hypoglycemia and severe ketoacidosis. Patients become more competent in both recognition and management of critical situations involving increased risk for severe hypoglycemia or diabetic ketoacidosis.

Blood glucose awareness training is an alternative standard self-management program approach that proved to decrease the rate of severe hypoglycemia in type 1 diabetes (15,16). In a 12-month

uncontrolled trial, blood glucose awareness training reduced the rate of severe hypoglycemia from 19.2 to 13.2 events · patient<sup>-1</sup> · year<sup>-1</sup> (17). Metabolic control was comparable to our analysis. However, comparison with our data is limited, since study populations and definitions of severe hypoglycemia differed. In addition, a main objective of the standard DTTP as used in the present study was the introduction of dietary freedom.

Before intervention, patients with high risk for severe hypoglycemia were in good glycemic control as reflected by GHb levels of 7.4%, which is comparable to the intervention group of the Diabetes Control and Complications Trial. Factors that contribute to the high risk for severe hypoglycemia include impaired awareness of hypoglycemia, low levels of C-peptide (18,19), and various psychological and behavioral processes (20), which might include a more risk-accepting lifestyle. Individuals of the smaller subgroup with high risk for severe ketoacidosis were in poor metabolic control before intervention and improved only slightly after the DTTP. Apart from false therapeutic decisions due to insufficient knowledge of diabetes self-management, incorrect insulin administration or application of damaged devices, lack of motivation, social and economical crises, and addictive or mental diseases that limit self-management skills have to be discussed (21,22). Data on these influences were not collected. However, because 72% of participants had no recurrent severe ketoacidosis the year after intervention, the DTTP seemed

**Table 2—Baseline and follow-up data of patients with one or no episodes versus two or more episodes of severe ketoacidosis during the year before the DTTP**

	Diabetic ketoacidosis during the year before the DTTP	
	One or no events · patient <sup>-1</sup> · year <sup>-1</sup>	Two or more events · patient <sup>-1</sup> · year <sup>-1</sup>
Patients (n)	9,488	95
Age at enrollment (years)	38.2 ± 14	31.5 ± 13
Mean duration of diabetes (years)	13.4 ± 10.9	12.3 ± 9.8
GHb at baseline (%)	8 ± 2	9.4 ± 2.8
GHb at follow-up (%)	7.3 ± 1.5	8.7 ± 2.5
Severe ketoacidosis at baseline (events · patient <sup>-1</sup> · year <sup>-1</sup> )	0.06 ± 0.2	3.25 ± 2.4
Severe ketoacidosis at follow-up (events · patient <sup>-1</sup> · year <sup>-1</sup> )	0.03 ± 0.2	0.58 ± 1.6
HD at baseline (days · patient <sup>-1</sup> · year <sup>-1</sup> )	5.6 ± 13.2	19.4 ± 23.1
HD at follow-up (days · patient <sup>-1</sup> · year <sup>-1</sup> )	3.5 ± 12.9	10.2 ± 22.6

Data are means ± SD. HD, hospital days.

to create solutions for at least some of these diverse problems.

Limitations arise from the study design. Subgroup analyses in general should be interpreted carefully. Because the present study does not include a control group, at least part of the observed changes may be due to the phenomenon of regression to the mean. However, the DTTP has been extensively studied, including randomized controlled trials with follow-up periods between 6 months and 2 years (4,7–9). In several long-term cohort studies in Germany and Austria, the DTTP was consistently followed by significant decreases in the risk of severe hypoglycemia and severe ketoacidosis and sustained, but less pronounced, improvements of glycemic control (5,10,23).

As discussed in an earlier article (6), overestimation of the benefits may also result from a biased data collection. Follow-up examination of patients by the members of the diabetes care team and the agreement to present outcome data in public at annual meetings may lead to framing of the data. Yet, with the regular supervision visits by peers and open discussion of results with the common mutual aim of improving the DTTP, this problem should be minimized. In addition, the administrative center performed plausibility checks and auditing of data on a regular basis (14).

In conclusion, we have shown that patients with type 1 diabetes and high risk of severe hypoglycemia and diabetic ketoacidosis may benefit from a standard self-management program for flexible intensive insulin therapy in routine care by reduction of acute complications without worsening metabolic control.

**Acknowledgments**—The working group for clinical diabetology has received funding for its annual meetings and the central office of the working group since 1993 from Sanofi-Aventis, Germany, and Roche Diagnostics, Germany.

We gratefully thank all nurses, dietitians, and physicians who generously participated on a volunteer basis, including reexamining patients and recording the data presented in this study.

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