Outpatient Assessment of Karlsburg Diabetes Management System–Based Decision Support

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OBJECTIVE — We sought to assess the benefit of the Karlsburg Diabetes Management System (KADIS) in conjunction with the continuous glucose monitoring system (CGMS) in an outpatient setting.

RESEARCH DESIGN AND METHODS — A multicentric trial was performed in insulin-treated outpatients ($n = 49$), aged 21–70 years, with a mean diabetes duration of 14.2 years. Subjects were recruited from five outpatient centers and randomized for CGMS- or CGMS/KADIS-based decision support and followed up for 3 months. After two CGMS monitorings, the outcome parameters A1C (%), mean sensor glucose of the CGMS profile (MSG) (mmol/l), and duration of hyperglycemia (h/day) were evaluated.

RESULTS — In contrast with the CGMS group (0.27 ± 0.67%), mean change in A1C decreased in the CGMS/KADIS group during the follow-up (−0.34 ± 0.49%; $P < 0.01$). MSG levels were not affected in the CGMS group (7.75 ± 1.33 vs. 8.45 ± 2.46 mmol/l) but declined in the CGMS/KADIS group (8.43 ± 1.33 vs. 7.59 ± 1.47 mmol/l; $P < 0.05$). Net KADIS effect (−0.60 [95% CI −0.96 to − 0.25%]; $P < 0.01$) was associated with reduced duration of hyperglycemia (4.6 vs. 1.0 h/day; $P < 0.01$) without increasing hypoglycemia. Multiple regression revealed that the A1C outcome was dependent on KADIS-based decision support. Age, sex, physician's specialty, diabetes type, and BMI had no measurable effect.

CONCLUSIONS — If physicians were supported by CGMS/KADIS in therapeutic decisions, they achieved better glycemic control for their patients compared with support by CGMS alone. KADIS is a suitable decision support tool for physicians in outpatient diabetes care and has the potential to improve evidence-based management of diabetes.

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A The Diabetes Complications and Control Trial–aligned A1C <7% is accepted as target for diabetes management (1). Benefits of lowering A1C in reducing the risk of or preventing late complications are well recognized (2,3). However, two-thirds of people with diabetes are currently above this target (4).

What are the reasons? Therapeutic intervention for normoglycemia has to consider complex cross-talking hormonal and metabolic pathways. Physicians' advice relies on official guidelines for diabetes management and on their judgement, and people with diabetes are compliant as much as possible. Nevertheless, achieving glycemic goals may sometimes result in an empiric, time-consuming, trial-and-error procedure. Therefore, physicians and computer scientists aimed to develop tools allowing simulation and prediction of blood glucose profiles in response to a changed therapeutic regimen under daily life conditions.

Several advisory systems have been propagated as effective tools for outpatient diabetes care (5). Achieved functionalities were prediction of blood glucose values, insulin dose adjustment, simulation of glucose profiles, and improvement of therapeutic regimen. However, the majority of decision support systems have thus far been developed for educational purposes (6–10). Only a few found acceptance and use by clinicians (6,11).

Among these advisory systems, KADIS, AIDA (Diabetic Software Simulation Program), and the Diabetes Advisory System (DIAS) are the only interactive model-based systems focused on interactive simulation of insulin/glucose profiles (9,10,12). While AIDA is a freeware computer program for educational purposes (9), DIAS can be used to predict the effects of changes in insulin dose or food intake (10). The glucose-predicting engine of Albisser et al. (6) provides short-term decision support for insulin-treated patients with respect to medication, diet, exercise, and stress. Similarly, Librae, which is written in a diary form, predicts blood glucose and was made as an educational tool for people with diabetes. MAIDS (Multiagent Intelligent Dosing System) is a recently described intelligent dosing system to manage combination therapy of insulin and oral antidiabetic drugs in type 2 diabetes (7).

KADIS is based on a mathematical model that describes the glucose/insulin metabolism in type 1 diabetes in the form of a coupled differential equation system (13–17). KADIS was expanded for application in type 2 diabetes by including an insulin controller describing basal and glucose-stimulated insulin secretion and the therapy with oral antidiabetic drugs. As therapy simulator, KADIS (12) calculates patient-specific parameters to assist physicians in choosing individual diabetes management regimens for optimizing glycemic control. The inputs for the program are patients' self-control data, such as blood glucose values, oral antidiabetic drugs and/or insulin therapy, carbohy-

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Abbreviations: ΔA1C, change in A1C; BU, bread exchange unit; CGMS, continuous glucose monitoring system; DIAS, Diabetes Advisory System; KADIS, Karlsburg Diabetes Management System; MSG, mean sensor glucose of CGMS profiles.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Patient demographics and study outcome*

Patient demographics	CGMS		CGMS/KADIS	
n	25		24	
Sex (female/male)	13/12		9/15	
Age (years)	48.4 ± 15.5		49.8 ± 11.3	
Diabetes duration (years)	13.4 ± 11.1		15.1 ± 10.0	
BMI (kg/m2)	28.5 ± 7.3		31.6 ± 6.4	
Diabetes type (1/2)	14/11		12/12	
Diabetes specialist/general practitioner	20/5		20/4	
Outcome parameter	Before	After	Before	After
ΔA1C (%)*	—	0.27 (−0.02 to 0.55)	—	−0.34 (−0.56 to −0.12)†
$A1C_{t0} < 7.0\%$	—	0.24 ± 0.64	—	0.03 ± 0.42
$A1C_{t0}$ 7.0–8.0%	—	0.74 ± 0.81	—	−0.23 ± 0.36†
$A1C_{t0} > 8.0\%$	—	−0.12 ± 0.36	—	−0.77 ± 0.55‖
A1C (%)	7.18 ± 1.42	7.44 ± 1.50	7.75 ± 1.21	7.41 ± 1.07‡
Mean sensor glucose (mmol/l)	7.75 ± 1.33	8.45 ± 2.46	8.43 ± 1.33	7.59 ± 1.47§
Hyperglycemia (h/day)¶	3.2 (0.4–6.0)	3.5 (1.0–9.0)§	4.6 (1.8–8.3)	1.0 (0.0–3.5)‡‖
Hypoglycemia (h/day)¶	0.0 (0.0–0.1)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
BU	11.8 ± 4.4	12.9 ± 5.3	12.6 ± 3.8	12.6 ± 3.9
Insulin (IU)¶	50.5 (35–66)	54 (33–71)	53 (37–77)	48 (35–72)

Data are means ± SD, mean (95% CI), or median (interquartile range). The euglycemic glucose range is defined as 4.4–8.9 mmol/l. Study subjects were classified according their baseline A1C ($A1C_{t0}$) into the groups <7% ($n = 17$), 7–8% ($n = 18$), and >8% ($n = 11$). *Mean (95% CI). †$P < 0.01$ vs. CGMS. ‡$P < 0.01$ and §$P < 0.05$ vs. before. ¶Mean (interquartile range). ‖$P < 0.05$ vs. CGMS.

drates of the meals, and exercise. The program is able to generate a virtual copy of glucose metabolism and allows interactive simulations of a person's daily therapeutic regime to optimize blood glucose profile (13–17). Moreover, KADIS can visualize 24-h absorption patterns of bread exchange unit (BU) intake and insulin equivalents of exercise, as well as action profiles of exogenous insulin and, in the case of type 2 diabetes, also of endogenous insulin and of oral anti-diabetic drugs in relation to the diurnal insulin sensitivity.

Previous KADIS studies used standard capillary glucose measurements as the data source, leading to longer acquisition periods. CGMS, however, provides extensive information about glycemic control by glucose readings every five min (18) and was therefore used as the source of glucose data in the present study.

We addressed the question of whether physicians in an outpatient setting can achieve significantly better glycemic control for their insulin-treated patients with KADIS-based decision support than without KADIS. For this purpose, physicians received decision support either in the format of CGMS profiles alone or in combination with KADIS advice, including dose and timing of insulin and amount and time schedule of food intake. The outcome measures, A1C, MSG, BU intake, and daily insulin application, were evaluated to assess the efficacy of KADIS decision support.

RESEARCH DESIGN AND METHODS

— The study was performed as a randomized, multicentric, prospective, and open-label trial in a case-control design. The study protocol was approved by the ethical review board at the University of Greifswald, Greifswald, Germany, and was conducted in accordance with the rules governing medical procedures in the European Community and the Declaration of Helsinki.

Before commencing the study, physicians were trained for handling the CGMS, and the KADIS report was explained in detail.

Patients were recruited in three general and two diabetes specialist outpatient practices by their physicians. They were asked for a prestudy examination within 4 weeks before the study and were given the opportunity to ask any question about the trial before being asked to provide written informed consent.

A simple randomization was used for assignment to the CGMS or CGMS/KADIS group. Patients with even random numbers, derived from a random number table, were assigned for the CGMS and patients with uneven random numbers for the CGMS/KADIS group. All patients were educated to use the CGMS monitors. At baseline, patients underwent a venous blood sampling for measurement of A1C and a 72-h CGMS monitoring under daily life conditions. CGMS data were downloaded and transferred to the Institute of Diabetes "Gerhardt Katsch" for analysis. Depending on the group to which the patient belonged, physicians received either CGMS data alone or CGMS data plus KADIS decision support report. CGMS data were presented as 24-h glucose profiles showing three individual sensor days and an MSG. The range of normoglycemia was highlighted, allowing the visual judgment of hypo- and hyperglycemic episodes, and a tabular presentation of self-control data obtained during the CGMS monitoring was provided. For the CGMS/KADIS group, the CGMS and self-control data were used to create KADIS-based recommendations consisting of CGMS data, a weak-point analysis of the glycemic status, recommendations for therapeutic adjustment, and the predicted 24-h glucose profile under optimized insulin therapy and suggested BU intake. During the 3 months of follow-up, the patients were entirely managed by their doctors and had one check-up during the 6 weeks after study entry. At the end of the study, CGMS monitoring and A1C measurements were repeated, and the study outcome was documented.

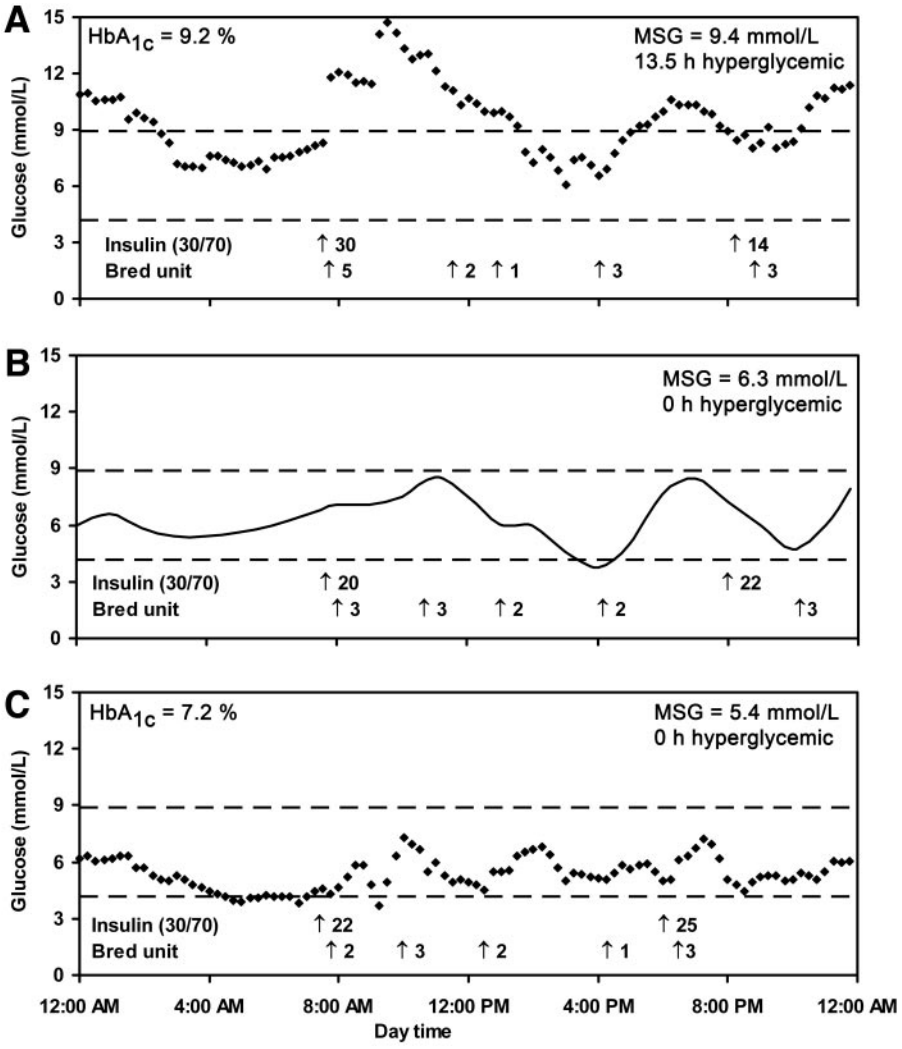

Figure 1—*Representative example for a CGMS/KADIS-based decision support of insulin-treated patients with diabetes. A: The dots represent the glucose values obtained by CGMS measurements. The profiles were obtained from a female patient aged 20 years, BMI 22.1 kg/m^2, who was diagnosed with type 1 diabetes 3 years ago. The mean sensor glucose was 9.4 mmol/l. The initial A1C was 9.2%. B: Decision support by KADIS recommended change of insulin application (dose and time) and decreased food intake over the day. Following these recommendations, the solid line represents the expected sensor glucose profile for this therapeutic adjustment, predicting 0 h/day in the hyperglycemic range. C: CGMS monitoring 3 months after supply of CGMS/KADIS-based decision support. The glucose profile is characterized by near normoglycemia. The patient achieved an A1C of 7.2%.*

Eligibility criteria

Male and female individuals with type 1 or type 2 diabetes who were at least 17 years old were included if they were insulin-treated European Caucasians, diagnosed with diabetes >1 year ago, and able to perform CGMS monitoring. They were not admitted to the study if any of the following criteria were present: *1*) inability to give consent, *2*) unwillingness to undertake blood glucose testing during the study, *3*) concurrent severe diseases, *4*) end-stage diabetes-related complications, *5*) insulin pump therapy, or *6*) participation in another clinical trial before the start of the study.

Primary and secondary outcome measures

The primary outcome measures were A1C and MSG. A1C was analyzed by the Bio-Rad Diamat analyzer system using ion-exchange high-performance liquid chromatography (normal range 4.6–6.0%). Secondary measures were the duration of hypo- and hyperglycemic excursions (h/day), BU, and daily insulin dose.

Sample size

Using a one-sided test at a 5% level of statistical significance, the trial was designed to have an 85% statistical power to detect a difference of 0.5% in change in A1C (ΔA1C) from baseline to end of trial between the CGMS and CGMS/KADIS group, with an assumed SD of 0.6. Expecting a loss to follow-up of 10%, 23 patients in each group were required.

72-h CGMS monitoring

CGMS (Medtronic MiniMed, Northridge, CA) monitoring was performed according to the standard Medtronic MiniMed operating guidelines. Glucose recording was calibrated against Accu-Chek monitors, which were weekly calibrated with Accu-Chek glucose standards. Patients were asked to enter at least four glucometer readings per day into the CGMS monitor for calibration and to make logbook entries of self-control data and any particular event (oral drug intakes, insulin administration, further therapeutic applications, food consumption, physical exercise, hypoglycemia symptoms, etc.) potentially affecting glucose control. The recorded data from each CGMS unit were downloaded using the MiniMed Solutions software (Medtronic MiniMed). Recorded profiles with less than three glucometer entries (calibrations) per day were disregarded.

KADIS-based decision support

Patient-centered KADIS decision support was generated in six steps: *1*) input of CGMS profile and self-control data (time and amount of food intake and insulin therapy), *2*) identification of patient-specific model parameters and analysis of actual weak points, *3*) simulation of glycemic effects of BUs and insulin therapies (dosage, type, and timing) according to the International Diabetes Foundation global and German guidelines (19,20), *4*) generation of KADIS-based recommendations, *5*) presentation of the results in a KADIS report visualizing weak points of glycemic control and detailing carbohydrates (amount and time of intake) and insulin (dosage, time, and type) required in silico to optimize the blood glucose curve of the patient, and *6*) application for therapeutic decisions by the physician.

Statistical analysis

All statistical analyses were carried out using the Statistical Package for the Social Sciences (version 12.0; SPSS, Chicago, IL). Results are given as means ± SD for normal distributed parameters or as median (interquartile range) for the non-normal distributed parameters: insulin dose, hyperglycemia, and hypoglycemia. MSG and the time for glucose values in

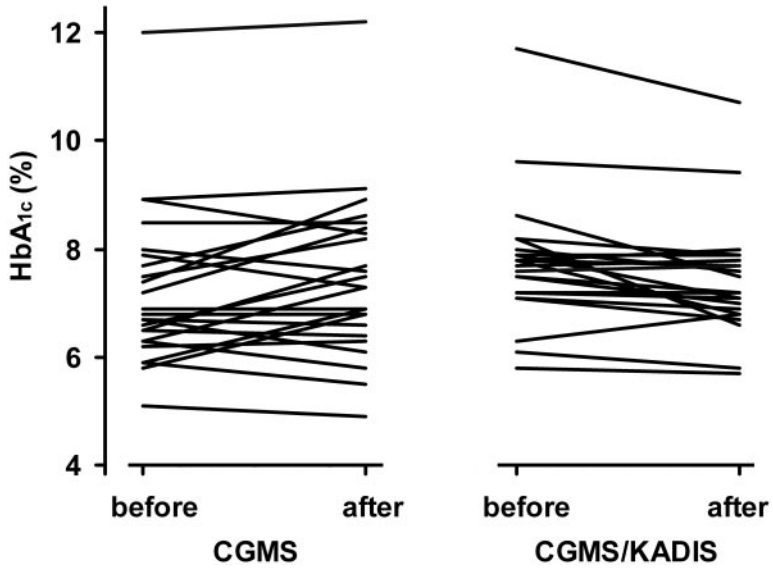

Figure 2—*A1C outcome presented for each study cohort in relation to A1C at baseline. The pre- and poststudy A1C values are given for every patient belonging to the CGMS- or CGMS/KADIS-supported group.*

hyperglycemic (>8.9 mmol/l) and hypoglycemic range (<4.4 mmol/l) were calculated from each continuously recorded glucose profile. ΔA1Cs are presented as mean change of the individual values with 95% CIs. Group comparisons were made using unpaired Student's *t* test or the Mann-Whitney *U* test as appropriate. Categorical variables were compared using χ^2 test. Within-group changes were tested by paired *t* test or Wilcoxon test as appropriate. Multiple regression analysis with stepwise forward selection was performed to reveal which variables were related to ΔA1C. Independent variables were A1C at study entry, specialty of physician (diabetes specialist or general practitioner), diabetes type, sex, age, BMI, and therapy support (CGMS or CGMS/KADIS). The level of statistical significance was set at $P = 0.05$.

RESULTS

Of the 49 subjects found eligible, 46 (24 in the CGMS and 22 in the CGMS/KADIS group) completed the study. Three subjects had incomplete first CGMS monitoring (one in the CGMS and two in the CGMS/KADIS group) and were excluded. Both study groups included type 1 and type 2 diabetic subjects in equal proportions. There were no significant differences in age, sex, diabetes duration, BMI, or insulin application between groups (Table 1).

Outcome measures

After follow-up for 3 months, patients of CGMS/KADIS-supported physicians achieved an overall ΔA1C of −0.34 ± 0.49% ($P < 0.01$%), whereas those of CGMS alone showed an increasing tendency (0.27 ± 0.67%). Reduction of A1C in the CGMS/KADIS-supported group was accompanied by a drop down of MSG from 8.43 ± 1.33 to 7.59 ± 1.47 mmol/l. The improved glycemic control was also reflected by reduction of hyperglycemia (Fig. 1; Table 1). Neither CGMS- nor CGMS/KADIS-based decision support affected hypoglycemia, insulin dosing, or carbohydrate intake. In addition, hypoglycemic episodes were neither reported by the patients nor by the physicians during the follow-up. The results of CGMS/KADIS-based therapy adjustment are exemplified for one subject in Fig. 1.

The A1C outcome for each cohort is demonstrated in Fig. 2. Multiple regression demonstrated that ΔA1C was related to KADIS advice ($\beta = -0.608$, SE = 0.175, $P = 0.001$, $R^2 = 21.5$%). Age, sex, diabetes duration, diabetes type, specialty of physician, and BMI had no additional influence. Multiple regression within the groups revealed that A1C outcome of the KADIS group was dependent on A1C at baseline ($\beta = -0.19$, SE = 0.08, $P = 0.031$, $R^2 = 47.7$%). In contrast, A1C outcome of the CGMS group was independent of A1C at baseline and of the other variables. ΔA1C (%) in relation to A1C at baseline is given in Table 1. The greatest effect was found in subjects with baseline A1C >8%. Here, CGMS/KADIS–based decision support had the highest impact on ΔA1C compared with CGMS alone. CGMS/KADIS further achieved a decrease in patients with baseline A1C between 7.0 and 8.0%, but there was no significant effect on ΔA1C if baseline A1C was <7.0% .

CONCLUSIONS — KADIS has the feature to identify the individual glycemic status of patients and is a patient-centered therapy simulator with the potential to assist physicians in improving diabetes control of insulin-treated diabetic outpatients. The question to be answered was whether physicians provided with CGMS profiles plus KADIS decision support achieve better glycemic control in their patients than those with CGMS alone. Therefore, we tested the hypothesis whether application of KADIS-based decision support results in significant reduction of A1C from baseline and MSG compared with CGMS-based support alone.

In this paper, we assessed the KADIS advisory system in outpatient settings. As the results demonstrate, physicians receiving CGMS/KADIS-based decision support were able to improve glycemic control of their patients within 3 months. Remarkably, the reduction of A1C by 0.6% in relation to CGMS alone and the prolonged period of euglycemia was not associated with an increased risk of hypoglycemia. Since the UK Prospective Diabetes Study has shown that each 1% reduction in A1C was associated with a 21% drop of diabetes-related death (2,3), our findings suggest a considerable potential for KADIS-based decision support to reduce late diabetic complications.

The A1C-lowering effect of KADIS-based decision support is in accordance with our previous study in insulin-treated diabetic patients, implementing self-control data as the only data source. Here, A1C declined by 2.6% (from 9.0 to 6.4%) within 21 months (21). Similar to our present findings, a meta-analysis of DIAS studies with 82 subjects revealed an A1C reduction of 1.2% (10), and after 6 months' application of a blood glucose prediction engine, A1C fell from 9.7 to 7.9% (6). However, it is conceivable that the outcome of a study also depends on A1C at baseline; comparison of our data with the above studies is thus limited. Indeed, we observed a pronounced A1C reduction in patients with A1C >8% at baseline. The potential for A1C improvement was moderate in our patients; 39% had A1C values ≥7%, and 24% had A1C values ≥8%. Nevertheless, physicians

supported by CGMS and KADIS achieved a reduction of A1C by −0.34%.

In contrast with reports by others who observed lowering of A1C after CGMS measurements (22–24), CGMS alone was insufficient to reduce A1C in our study, supporting the notion that CGMS is of little benefit to the practitioner. From our present data, the following question arises: What was the advantage of combined CGMS/KADIS decision support compared with CGMS alone? Apparently, CGMS profiles alone provided limited information for physicians because of difficulties in interpreting the findings, whereas KADIS reports contain detailed recommendations on how to improve glycemic control based on the hormonal and glycemic status identified individually for each patient.

Our findings suggest that the KADIS information effectively guided physicians in therapeutic decision making and allowed their outpatients to achieve improved A1C. CGMS and KADIS used in combination can improve glycemic control. Here, the value of CGMS is to optimize KADIS by providing a great number of glucose values.

In conclusion, our study implies that physicians who refer patients for KADIS will receive the optimal insulin dosing and BU intake to efficiently manage their patients. This circumvents time-consuming empiric procedures, especially for general practitioners, to find out the appropriate therapeutic adjustment to achieve near-normal glycemic control. The ability of KADIS to simulate the outcome of therapeutic adjustments provides a considerable potential and may allow KADIS to become a powerful decision-making aid in diabetes care.

However, a larger randomized trial with longer follow-up periods and various therapy groups needs to be carried out to investigate long-term effects of KADIS-based decision support and to answer the question of whether patients who are not using insulin might equally benefit.

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