Hypoglycemia: An Excuse for Poor Glycemic Control?

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What is the evidence supporting the benefits of intensified glycemic control for diabetic patients? The Diabetes Control and Complications Trial (DCCT) and the Stockholm Diabetes Intervention Study (SDIS) showed that intensive therapy significantly reduced the incidence and progression of microvascular complications in patients with type 1 diabetes. In the DCCT, during a mean of 6.5 years, diabetic retinopathy developed or progressed in 14% of patients with type 1 diabetes who were treated intensively compared with 32% of patients treated conventionally. Nephropathy and neuropathy also developed or progressed at lower rates in the intensively treated group.[1–3]

The United Kingdom Prospective Diabetes Study (UKPDS) and the Kumamoto study determined that stricter glycemic control could be useful in delaying the onset and progression of diabetic microvascular complications in patients with type 2 diabetes.[4,5] The Wisconsin Epidemiological Study of Diabetic Retinopathy showed that higher levels of glycemia are related to decreasing quality of life.[6]

Analyses of data from these and other studies suggest that, by whatever means, intensive therapy with the goal of achieving normoglycemia should be implemented as early as possible in patients with either type 1 or type 2 diabetes. Theoretically, this could improve patient quality of life and save medical resources (Figure 1). Thus, there is no longer an excuse to not intensively treat patients with diabetes, especially younger patients with a recent onset or short duration of the disease. These are the patients who stand to benefit the most from maintenance of long-term normoglycemia.

Danger of hypoglycemia is the customary reason given for not achieving the glycemic goals. Iatrogenic hypoglycemia is classified as either *1*) asymptomatic or biochemical, *2*) mild to moderate, or *3*) severe. The DCCT definition of severe hypoglycemia as being an episode severe enough to require help from another person has been adopted in many subsequent studies.

Throughout this review, we will concentrate on severe hypoglycemia because of the subjectivity of reports of mild and moderate hypoglycemia and their imperfect correlation with biochemical hypoglycemia. For example, in a study[7] of 66 randomly selected insulin-dependent diabetic patients on conventional insulin regimens, the weekly frequencies of symptomatic and biochemical hypoglycemia were 0.99 and 1.75 per patient, respectively. Biochemical hypoglycemia was present in only 29% of the symptomatic episodes, and symptomatic hypoglycemia accompanied a mere 16% of the biochemical episodes.

IN BRIEF

Although long-term maintenance of normoglycemia can prevent the onset and delay the progression of the microvascular complications in diabetes, a large percentage of diabetic patients continue to have poorly controlled glucose levels. The risk of hypoglycemia is a real obstacle to achieving glucose targets in type 1 diabetes. However, risk of severe hypoglycemia in type 2 diabetes is minimal and should not be used as an excuse for failing to achieve glycemic goals. This article reviews the incidence of severe hypoglycemia in the major diabetes trials, the results of attempts to optimize glycemia to date, and the ways to ameliorate severe hypoglycemia in the treatment of both type 1 and type 2 diabetes.

How well did the major diabetes trials control glycemia?

Current guidelines for glycemic control are mostly derived from several large-scale trials that tested the hypothesis that more intensive glycemic control could either prevent or delay the classic diabetic complications (Figure 2). What was the actual level of glycemia achieved in the studies?

- The mean HbA_{1c} in the DCCT was 7.2% (mean capillary blood glucose of 155 ± 30 mg/dl, roughly twice that of nondiabetic individuals) in the intensive group. Fewer than 5% of those treated intensively maintained normal HbA_{1c} (<6.05%). HbA_{1c} was ~9% in the conventional group.

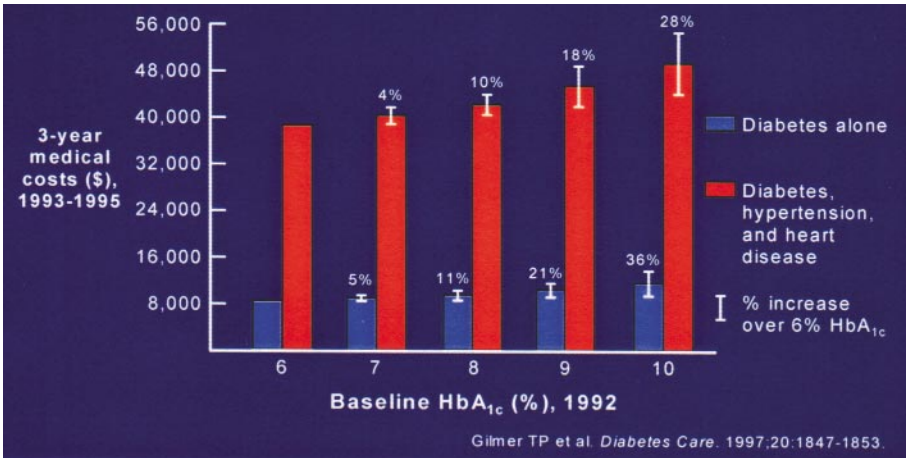

Figure 1. Complications of diabetes: better glycemic control reduces health care costs. Reproduced with permission from Gilmer T, O'Conner P, Manning W, Rush W: The cost to health plans of poor glycemic control.* Diabetes Care *20:1847–1853, 1997.

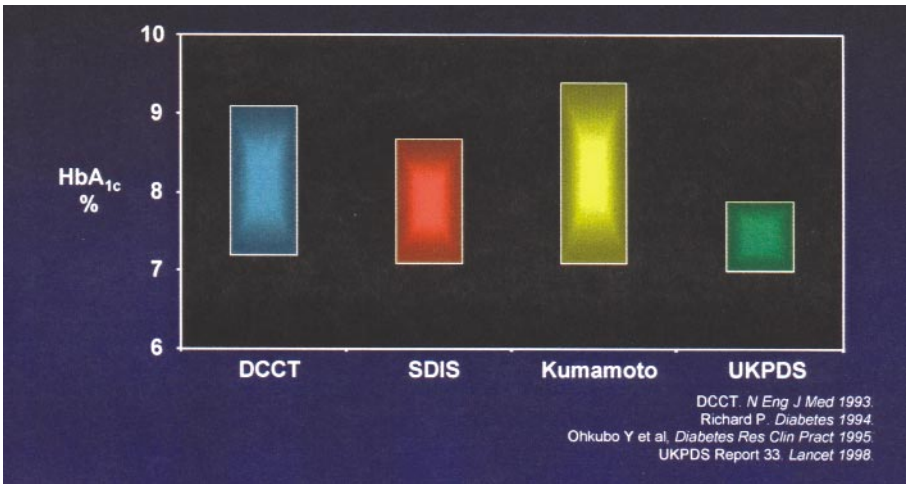

Figure 2. HbA1c differences between intensively and conventionally treated patients in major clinical trials, with baseline to endpoint HbA_{1c} level in type 1 diabetes (DCCT, SDIS) and type 2 diabetes (UKPDS, Kumamoto).

- The mean HbA_{1c} in the SDIS was 7.1% in the intensively treated patients and ~8.8% in the conventionally treated patients.
- The mean HbA_{1c} in the UKPDS was 7% in the intensively treated group and 7.9% in the conventionally treated group.
- The mean HbA_{1c} in the Kumamoto study was 7.2% in the intensively treated group and 9.4% in the conventionally treated group.

Based on these interventions studies, the current consensus is that HbA_{1c} >8% is unacceptable, <8% serves as a minimal target, <7% is the American Diabetes Association goal,[8] and <6% is the optimal target.

How good are we at achieving glycemic control?

In spite of all the recommendations, we still are not doing very well. Average HbA_{1c} among U.S. diabetic patients is estimated to be ~8.5% (R. Kahn, ADA Provider Recognition Program Study, unpublished observations). The level of implementation of diabetes care in the United States remains suboptimal. Among adults with diabetes who are >20 years of age and participated in the third National Health and Nutrition Examination Survey (NHANES III), 44.6% had HbA_{1c} concentrations <7%, 63% had concentrations <8%, and 85.9% had concentrations <10%.[9]

Why are we not meeting the goals?

The usual answer is that hypoglycemia is the major limiting factor in achieving glycemic goals. For type 1 diabetes, at the current time, it is probably true that achieving normoglycemia (HbA_{1c} <6%) is fraught with the danger of hypoglycemia. Severe hypoglycemia is a frightening condition associated with significant morbidity and accounting for up to 4% of deaths in type 1 diabetic patients.

Many physicians do not recommend intensive treatment because they are concerned about inducing hypoglycemia. Patients are reluctant to undertake such an intensive therapy because they fear the increased risk of hypoglycemia. The relevant issue is whether we can devise safer ways to lower blood glucose.

Hypoglycemia is a real obstacle for patients with type 1 diabetes.

Unfortunately, several barriers still prevent the majority of patients with type 1 diabetes from being on intensive treatment. Some of the obvious reasons are economical, cultural, and organizational. However, an additional barrier is the fear of severe hypoglycemia, which has been reported to be more frequent in intensively treated patients than in those treated conventionally.

1. The DCCT reported that, despite efforts to reduce the risk of hypoglycemia during intensive therapy, a threefold increase in severe hypoglycemia persisted with intensive versus conventional therapy during the trial (62 vs. 19 episodes per 100 patient-years, respectively).[2] The best predictor of severe hypoglycemia was higher initial HbA_{1c} that dropped very quickly toward the normal

range. Several other risk factors have been noted, including male sex, adolescence, and higher insulin doses, but these associations were of minor significance. The presence or absence of autonomic neuropathy was not important.[10] An additional risk factor for the development of hypoglycemia in some patients is the administration of other medications, such as β-blockers.[2]

2. The SDIS showed a 2.5 times greater incidence of severe hypoglycemia among intensively treated patients.[3]
3. In a meta-analysis of 14 controlled, randomized trials, a combined odds ratio for severe hypoglycemia of 2.99 (range 2.45–3.63) indicated a substantial and statistically significant (P <0.0001) increase in the risk of suffering one or more episodes of severe hypoglycemia during attempts at intensive therapy. The risk of severe hypoglycemia was correlated with the degree of glycemia normalization.[11]
4. Studies using continuous glucose monitoring devices have revealed that type 1 diabetic patients with presumed hypoglycemia awareness do not recognize 40–60% of all hypoglycemic episodes, even when fingerstick blood glucose measurements are performed 4–7 times per day.[12,13]

Why does hypoglycemia occur more in type 1 diabetes?

The release of glucagon and epinephrine is the most important component of the counterregulatory response to insulin-induced hypoglycemia. Glucagon loss occurs early in the natural history of type 1 diabetes, and it is irreversible. Epinephrine response becomes impaired in many type 1 diabetic patients, especially in long-term diabetes, and it is largely due to antecedent recurrent iatrogenic hypoglycemia.[14]

How can we ameliorate severe hypoglycemia in the intensive treatment of type 1 diabetes?

The best attempts to decrease the risk of severe hypoglycemia have been undertaken by Bott and associates[15] and Bolli and associates.[16] These investigators showed that it is possible to decrease HbA_{1c} concentrations with intensive therapy while decreasing the risk of severe hypoglycemia by following these relatively simple guidelines:

1. Monitor blood glucose levels frequently.

Frequent blood glucose monitoring (at least as many times a day as the number of different insulins injected by the patient) is suggested. Unfortunately, blood glucose monitoring is expensive. This poses a real problem for many patients in United States and Europe and even more so for those in developing countries.

Titration of the meal-time insulin dose for patients using regular insulin is based typically on glucose levels before the following meal (or about 4–5 h post-meal). Titration of short-acting insulin analogs (lispro [Humalog] or aspart [Novolog]) is based on the 2-h post-meal blood glucose level. Titration of bedtime NPH is typically based on the fasting blood glucose level.

2. Use physiological models of insulin replacement.

Physiological insulin replacement is based on the idea that overall glycemic control is best achieved by mimicking the way normal human insulin affects blood glucose levels in people without diabetes. Normal insulin profiles show that blood insulin levels rise rapidly after meals. They reach their maximum level within 10 min, with a subsequent swift decline as peak glucose concentrations are reached. In the postprandial stage, about 2–4 h after food intake, insulin levels are just above fasting blood glucose concentrations. In patients with diabetes, the absence of the rapid insulin response following meals needs correction.

Preventing hypoglycemia is easier if insulin delivery mimics the physiology of endogenous insulin secretion of normal subjects. This can be best achieved with continuous subcutaneous insulin infusion (CSII, or insulin pump) therapy. However, for several reasons including cost, pumps are not a practical solution for most patients with type 1 diabetes.

Multiple daily insulin injections (MDIs) are a good alternative to insulin pump therapy. It is important to emphasize that this model of treatment may be used successfully to prevent hypoglycemia both during the day and at night.

Use of NPH insulin at bedtime. At least half of all hypoglycemic episodes occur at night, and most of them are not recognized. NPH insulin exhibits an early peak 2–5 h after subcutaneous injection. This means that if NPH insulin is injected at dinner time (5:00–7:00 p.m.), it peaks approximately at midnight and increases the risk of nocturnal hypoglycemia. The best approach for solving this problem is to divide the evening dose of insulin into a dose of short-acting insulin analog at dinner (or of regular insulin 30–45 min before dinner) and a smaller dose of NPH at bedtime. This should decrease the risk of hypoglycemia.

Use of insulin glargine at bedtime. Glargine is an extended-action biosynthetic human insulin. Four large clinical trials of up to 28 weeks' duration have shown that a single bedtime dose of glargine, in combination with preprandial short-acting insulin, is as effective or more effective than once or twice daily NPH plus short-acting insulin in improving glycemic control in patients with either type 1 or type 2 diabetes. A lower incidence of hypoglycemia, especially at night, has been noted with glargine use.[17,18]

Use of a short-acting insulin analog with meals. The short-acting insulin analogs (lispro and aspart) are quite appealing because they can be injected at mealtime and still improve postprandial blood glucose levels. Their benefit on hypoglycemia is small but well documented, especially for severe and nocturnal hypoglycemia. Many studies[19–21]

have examined lispro's effect on the risk of hypoglycemia in intensive treatment of type 1 diabetes using either CSII or MDI therapy. In subjects with identical HbA_{1c} concentrations, lispro decreases the risk of hypoglycemia as compared with human regular insulin. Its greatest effect is on nocturnal hypoglycemia, which was reduced threefold in one study.[22]

The duration of action of lispro is shorter than that of regular insulin, however, and simply substituting lispro for regular insulin unit for unit could result in insulin deficiency and, therefore, greater hyperglycemia before meals. This is presumably the reason why in most studies, the better postprandial blood glucose control achieved with lispro has not resulted in lower HbA_{1c} concentrations.[23]

Thus, when lispro is used instead of regular insulin for mealtime coverage, more appropriate replacement of basal insulin is required to improve mean daily blood glucose and HbA_{1c} concentrations.[24] This may be easily solved with CSII, but it is more complicated with MDI because NPH might need to be injected up to three times daily.

3. Advise patients to avoid between-meal snacks.

With current MDI regimens involving regular and rapid-acting insulins, snacks are not only not necessary, but can actually be detrimental to blood glucose control because they increase blood glucose before the next meal. If the resulting hyperglycemia leads to more insulin use and weight gain, the final outcome might not be desirable.

Several factors that affect glycemic response to carbohydrate intake should be taken into consideration when dealing with hypoglycemia. These include:

- the digestion and absorption process
- the physical state of the food item (e.g., whole grain vs. ground rice; the effects of cooking)
- the fiber content of the meal, which can delay gastric emptying, alter transit time in the small intestine, and insulate carbohydrate from digestive enzymes
- other nutritional components of the meal (fat and protein) that can potentially slow down the rate at which carbohydrate turns to glucose.

Several studies have reported that protein ingestion does not raise the circulating glucose concentration or raises it only modestly.[25] A study comparing the effectiveness of a protein-enriched snack with that of a plain carbohydrate snack for the treatment of hypoglycemia showed that the protein adds calories but does not prolong protection against subsequent hypoglycemia.[26]

4. Consider the potential role of continuous glucose monitoring.

Identifying hypoglycemia through the use of a continuous glucose monitoring system (CGMS) can minimize the frequency of hypoglycemia and help patients attain their glycemic goals. In contrast to relying on multiple fingerstick blood glucose measurements taken throughout the day, using the CGMS allows clinicians to identify patients at risk of severe hypoglycemia and to discern and address patterns of glucose fluctuations that occur throughout the day. Unexpected hypoglycemia can then be diagnosed and handled with adjustments in the treatment regimen,[27] which should increase the safety of insulin therapy considerably.

5. Provide adequate education.

Time spent with patients is the most valuable way to decrease HbA_{1c} concentrations and the frequency of severe hypoglycemia. Unfortunately, patients are many, and providers are few. Diabetes educators, although essential for the job, cannot be fully delegated the complicated tasks associated with intensive diabetes management.

The most important job that providers should undertake, in addition to providing cutting-edge medical treatment, is to transmit to their patients the motivation and enthusiasm to carry the burden of intensive therapy. Providers need to stay in close contact with their patients to be able to alter treatment regimens frequently based on blood glucose values in order for patients to realize the full benefit of such an expensive (in terms of time, effort, energy, and dollars) therapy.

The results of the above strategy to maintain long-term near-normoglycemia, to minimize the risk of recurrent hypoglycemia, and to prevent hypoglycemia unawareness can be impressive.[28] The frequency of hypoglycemia in some studies[15,16] was ~60 times less than in the DCCT. However, we need to watch out for high-risk individuals. These include patients with a history of severe hypoglycemia; those with longer duration of diabetes; those with higher insulin doses at baseline; those with lower HbA_{1c} concentrations or a recent decrease in HbA_{1c} concentration; those with concomitant alcohol or β-blocker use; those who do not comply with recommendations to carry an emergency carbohydrate supply; and those with a younger age at onset of diabetes.

Severe hypoglycemia is rare in type 2 diabetes.

The risk of severe hypoglycemia in patients with type 2 diabetes is minimal and should not be used as an excuse for failing to achieve glycemic goals. One reason that hypoglycemia poses less of a threat in type 2 diabetes is that glucagon and epinephrine deficits are much less prominent.

Results of several large studies in patients with type 2 diabetes support this notion.

1. In the VA Cooperative Study, severe hypoglycemic reactions among intensively treated patients were extremely rare and not significantly different from those among conventionally treated patients.[29]
2. In the UKPDS, newly diagnosed patients with type 2 diabetes and a body mass index of 27–28 kg/m^2 were randomly assigned to conventional treatment with diet or one of

several intensive treatment regimens. Severe hypoglycemia occurred in 0.7% per year for those allocated to sulfonylurea therapy, 2.3% per year for those allocated to take insulin, 0.1% per year for those allocated to take metformin (Glucophage), 0.3% per year for those allocated to take both metformin and sulfonylurea, and, surprisingly, 0.03% per year for those allocated to diet therapy alone.[30]

3. The Kumamoto study, which evaluated insulin-requiring non-obese Japanese patients with type 2 diabetes, showed no severe hypoglycemia over 8 years in either the intensively or the conventionally treated group.[5] The difference in the rate of severe hypoglycemia between the UKPDS and the Kumamoto study might be explained by *A*) the difference in insulin doses (0.4 units/kg in the Kumamoto study versus 0.2 units/kg for non-obese and 0.5 units/kg for obese subjects in the UKPDS) and/or, *B*) the difference in frequency of routine clinic visits (every 3–4 months in the UKPDS versus every 2 weeks in the Kumamoto study).

How does intensive glycemic control affect the risk of hypoglycemia in type 2 diabetes?

All hypoglycemic agents are theoretically capable of producing severe hypoglycemia. Proper patient selection, drug dosage, and instructions are important factors in avoiding severe hypoglycemia. Renal or hepatic insufficiency may increase drug blood levels. Elderly, debilitated, or malnourished patients and those with adrenal or pituitary insufficiencies are susceptible to hypoglycemic reactions.

Although hypoglycemia is sometimes listed as a manifestation of hypothyroidism, it is rarely a sign of isolated thyroid hormone deficiency. The presence of hypoglycemia in a patient with hypothyroidism should suggest the presence of hypopituitarism. The occurrence of hypothyroidism in a patient with insulin-requiring diabetes may result in some diminution in exogenous insulin requirement because of both a decreased rate of insulin degradation and a decreased appetite.[31,32] Conversely, correction of hypothyroidism in an insulin-requiring diabetic patient usually necessitates an increase in insulin dose.

Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, with alcohol ingestion, or when a combination of glucose-lowering drugs is used. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking β-blockers.

Risk of severe hypoglycemia with sulfonylureas. In a 4-year retrospective study of 14,000 patients with type 2 diabetes over 65 years of age and treated with different sulfonylureas,[33] episodes of severe hypoglycemia were rare (1.23 episodes per 100 patient-years). The incidence was highest among those patients taking glyburide (Diabeta, Micronase, Glynase) and lowest among those taking tolbutamide (Orinase) (1.66 vs. 0.35 episodes per 100 patient-years, respectively). Other shorter-acting sulfonylureas, such as tolazamide (Tolinase) and glipizide (Glucotrol), were also associated with a lower incidence of severe hypoglycemia,[34] whereas its incidence with chlorpropamide (Diabinese) was similar to that found with glyburide. Patients recently discharged from the hospital were at the highest risk (4.5 episodes per 100 patient-years).

The UKPDS reported severe hypoglycemia occurring at a rate of 0.7% per year among 922 patients newly diagnosed with type 2 diabetes and assigned to treatment with sulfonylureas. The cumulative incidence of severe hypoglycemia occurring in this group over the 6 years of study was 3.3%. Unfortunately, hypoglycemia was not corroborated by blood glucose determination in this study, and the details of the episodes were not provided. Interestingly, an incidence of severe hypoglycemia of 0.03% per year was reported among patients who were treated with diet alone. This raises questions about the causes of these episodes and reinforces the importance of carefully documenting glucose levels during apparent hypoglycemic episodes in type 2 diabetes.

Risk of severe hypoglycemia with repaglinide (Prandin) and nateglinide (Starlix). The risk of hypoglycemia seems to be minimal with both repaglinide and nateglinide. For example, in a study of 66 patients with type 2 diabetes treated with repaglinide for 18 weeks,[35] there were no reports of severe hypoglycemia.

Repaglinide may be a good choice for patients who miss or postpone meals. In a study involving type 2 diabetic patients treated with repaglinide or glyburide, there were no hypoglycemic episodes in repaglinide-treated patients on the days when lunch was omitted compared to six hypoglycemic episodes in the glyburide-treated group on days when lunch was omitted.[36]

In a combination study of repaglinide and metformin, there were no severe hypoglycemic episodes among 27 patients within the 3-month maintenance period.[37] In another comparison study of nateglinide and glyburide in previously diet-treated patients with type 2 diabetes, nateglinide selectively enhanced early insulin release and provided better mealtime glucose control with less insulin exposure and less hypoglycemia than glyburide.[38]

Risk of severe hypoglycemia with metformin, α-glucosidase inhibitors (e.g., acarbose [Precose] and miglitol [Glyset]), and thiazolidinediones (e.g., rosiglitazone [Avandia] and pioglitazone [Actos]). These are antihyperglycemic rather than hypoglycemic drugs. Severe hypoglycemia does not occur in patients receiving these agents alone under usual circumstances. It could, however, occur during concomitant use with hypoglycemic agents such as insulin, sulfonylureas, repaglinide, or nateglinide.

Can we minimize severe hypoglycemia in intensively treated patients with type 2 diabetes?

Severe hypoglycemia is generally rare. However, high-risk individuals might be those with *1*) a history of severe hypoglycemia, *2*) negative C-peptide levels, *3*) a low level of diabetes education, or *4*) hypoglycemia unawareness. The risk also increases with age and longer duration of diabetes.

A number of therapeutic regimens that are similar to the type 1 diabetes regimens mentioned earlier can minimize the frequency of severe hypoglycemia as well as that of nocturnal hypoglycemia. To recap, for patients who are on the conventional regimen of regular human insulin and NPH insulin twice daily, taking the evening dose of NPH at bedtime instead of before the evening meal can reduce the frequency of severe nocturnal hypoglycemia. Rapid-acting insulin analogs injected at the time of the evening meal can considerably reduce the risk of nocturnal hypoglycemia compared with regular insulin.[39] Insulin glargine at bedtime is at least as effective as once- or twice-daily NPH in improving glycemic control and carries a lower incidence of hypoglycemia, especially at night.[17]

Conclusions

Patient education, empowerment, self-monitoring of blood glucose, more flexible and physiological insulin replacement regimens, and professional support can all minimize the frequency of severe hypoglycemia. This labor-intensive approach, however, will require commensurate insurance reimbursement of the professionals delivering diabetes management based on the time spent with patients and the outcomes achieved.

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