REVIEW

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Emerging care for type 2 diabetes: Using insulin to reach lower glycemic goals

ABSTRACT

Intensive control of blood glucose reduces the incidence and progression of many of the complications of type 2 diabetes. Newer insulin formulations that approach normal physiologic patterns have made it possible to achieve glycemic goals without excessive hypoglycemia.

KEY POINTS

In view of recent evidence in favor of strict glycemic control, the American Diabetes Association has lowered its recommended glycemic thresholds for the diagnosis of prediabetes and for goals of treatment.

Achieving lower glycemic targets often requires using insulin therapy earlier and more aggressively than in the past.

Physicians may directly or indirectly communicate negative messages about insulin therapy by implying that it is dangerous or that it is a sign of failure on the part of the patient to comply with treatment.

New insulin preparations have pharmacokinetic patterns that more closely mimic physiologic insulin patterns than do those of older preparations, resulting in better glycemic control and fewer adverse effects.

*The authors have indicated that they have received grant or research support from Aventis Pharmaceuticals.

DIABETES EXPERTS, armed with a better understanding of the natural history of type 2 diabetes, are advocating identifying and treating patients earlier in the disease process to slow its progression and to decrease the risk of its complications.[1]

Specifically, thresholds for the diagnosis of prediabetes (formerly called impaired fasting glucose) have been lowered, and goals for glycemic control have been made tighter.[2]

To meet these lower glycemic targets, many patients will need to add on insulin therapy when oral antidiabetic agents alone no longer suffice.[3] Fortunately, we now have several new insulin products that pose a substantially lower risk of hypoglycemia compared with older human insulin formulations and that control blood glucose levels better.[3]

In addition, standards of care now call for modifying other risk factors (eg, high blood pressure, elevated lipids) to help decrease the risk of complications of diabetes.[4]

TYPE 2 DIABETES IS PROGRESSIVE

Type 2 diabetes is a progressive disease of increasing insulin resistance and decreasing beta-cell function.

The preclinical, asymptomatic stage is characterized by insulin resistance with normal plasma glucose levels and relative hyperinsulinemia. As beta-cell function declines, the increased insulin production no longer suffices to maintain glucose homeostasis, and patients typically progress to prediabetes, with impaired glucose tolerance, characterized pri-

TABLE 1

Glycemic thresholds for diagnosis of type 2 diabetes

DIAGNOSIS	PLASMA GLUCOSE LEVEL	
	FASTING	2-HOUR POSTLOAD
Normal	< 100 mg/dL (< 5.6 mmol/L)	< 140 mg/dL (< 7.8 mmol/L)
Prediabetes	100–125 mg/dL (5.6–6.9 mmol/L)	140–199 mg/dL (7.8–11.0 mmol/L)
Diabetes*	≥ 126 mg/dL (≥ 7.0 mmol/L)	≥ 200 mg/dL (≥ 11.1 mmol/L)

*Must be confirmed on a separate day.

ADAPTED FROM RECOMMENDATIONS OF THE AMERICAN DIABETES ASSOCIATION.[2,12,13]

marily by elevated postprandial and fasting glucose levels. Chronic symptomatic hyperglycemia develops when insulin levels decline markedly due to beta-cell failure.[1]

Progression from insulin resistance to overt type 2 diabetes mellitus may not be inevitable; it is possible to slow disease progression before reaching a level of irreversible beta-cell failure.[1] In recent years, the trend has been to start treatment in patients with prediabetes (an estimated 20 million people in the United States between the ages of 40 and 74),[5] rather than to delay treatment until uncontrolled blood glucose levels lead to chronic complications.[1]

Progression from insulin resistance to overt type 2 diabetes may not be inevitable

CLINICAL PRACTICE RECOMMENDATIONS

Importance of tight glucose control

In 1993, the Diabetes Control and Complications Trial[6] clearly demonstrated that keeping glucose at near-normal levels could delay the onset or slow the progression of microvascular complications (ie, retinopathy, nephropathy, neuropathy) in patients with type 1 diabetes mellitus.

The UK Prospective Diabetes Study later confirmed that intensive blood glucose control also decreases the risk of microvascular disease in patients with type 2 diabetes.[7]

Diagnostic thresholds have been lowered

Over the past decade, recommended glycemic thresholds for diagnosis and intervention have been lowered in light of evidence supporting early tight glycemic control.

In 1979, an international working group sponsored by the National Diabetes Data Group of the National Institutes of Health (NIH) developed clinical criteria for diabetes and other categories of glucose intolerance.[8] Any of the following was considered diagnostic of diabetes:

- In adults, classic symptoms of diabetes such as polyuria, polydipsia, ketonuria, and unexplained weight loss together with unequivocal hyperglycemia;
  or
- Fasting plasma glucose concentrations of 140 mg/dL (7.8 mmol/L) or greater on more than one occasion;
  or
- Sustained elevated plasma glucose levels during an oral glucose tolerance test, ie, 200 mg/dL (11.1 mmol/L) or higher on at least two occasions up to 2 hours after ingesting the glucose dose, regardless of the fasting level.

In 1997, in response to new knowledge about the etiology and pathogenesis of diabetes, the International Expert Committee re-examined the earlier diagnostic criteria from the NIH[9] and the World Health Organization.[10] In the 1997 criteria,[11] any of the following, confirmed on a subsequent day, is diagnostic of diabetes:

- Symptoms of diabetes and a casual plasma glucose concentration 200 mg/dL (11.1 mmol/L) or greater (the classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss; casual means any time of day without regard to the last meal);
  or
- Fasting plasma glucose 126 mg/dL (7.0 mmol/L) or greater (fasting is defined as no caloric intake for at least 8 hours);
  or
- Plasma glucose 200 mg/dL (11.1 mmol/L) or greater 2 hours after an oral glucose load during a glucose tolerance test. The test should be performed as described by the World Health Organization,[9] using the equivalent of anhydrous glucose 75 g dissolved in water. (However, fasting plas-

TABLE 2

Goals of glycemic control in type 2 diabetes

TEST	AMERICAN DIABETES ASSOCIATION	AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS
Hemoglobin A_{1c}	< 7.0%*	< 6.5%
Preprandial plasma glucose	90–130 mg/dL (5.0–7.2 mmol/L)	< 110 mg/dL (< 6.1 mmol/L)
Postprandial plasma glucose†	< 180 mg/dL (< 10.0 mmol/L)	< 140 mg/dL (< 7.8 mmol/L)

*Referenced to a nondiabetic range of 4.0% to 6.0% using a Diabetes Control and Complications Trial (DCCT)-based assay.[15]
†Postprandial glucose measurements should be made 2 hours after the beginning of the meal.

ADAPTED FROM RECOMMENDATIONS FROM THE AMERICAN DIABETES ASSOCIATION AND THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS.[12,14]

ma glucose is the preferred screening and diagnostic test since it is easier to use, more acceptable to patients, and less expensive than an oral glucose tolerance test.[12])

Further, the committee established a criterion for *impaired fasting glucose:* 110 to 125 mg/dL (6.1–6.9 mmol/L). Normal fasting glucose was lower than 110 mg/dL (6.1 mmol/L).

In 2003, a newly organized expert committee convened to consider data published after the 1997 report, and issued revised criteria (TABLE 1).[2,12,13]

On the basis of epidemiologic data, the 2003 committee determined that the defined limit of 110 mg/dL for impaired fasting glucose weakened the power of fasting plasma glucose as a predictor of future diabetes.[2] Accordingly, it redefined the category as a fasting plasma glucose concentration of 100 to 125 mg/dL (5.6–6.9 mmol/L) and called it *prediabetes*.

Therefore, a normal fasting glucose value is now defined as less than 100 mg/dL (5.6 mmol/L); the criteria to diagnose diabetes remain as previously defined.

Glycemic goals

Hemoglobin A_{1c} < 7%. The American Diabetes Association (ADA) recommends using glycosylated hemoglobin (hemoglobin A_{1c}) values to track glycemic control.[12]

Epidemiologic data show that there is no hemoglobin A_{1c} level below which the risk of complications does not continue to decrease.[12] Although the ADA currently recommends a hemoglobin A_{1c} goal of less than 7.0% for most patients, this is not a "normal" level observed in nondiabetic people.[12] Accordingly, a more stringent goal (ie, < 6.5%) can be considered on a case-by-case basis at the physician's discretion (TABLE 2).[12,14,15]

Normal fasting plasma glucose is now < 100 mg/dL

The ongoing Action to Control Cardiovascular Risk in Diabetes (ACCORD) study[16] is testing whether three complementary strategies will reduce the development and progression of macrovascular complications in patients with type 2 diabetes: lowering hemoglobin A_{1c} to less than 6%; lowering systolic blood pressure to less than 120 mm Hg; and lowering low-density lipoprotein cholesterol (LDL-C) to between 40 and 100 mg/dL using fibrate-plus-statin therapy. The results will help to clarify the risks and benefits of targeting lower hemoglobin A_{1c} goals.

Preprandial plasma glucose 90–130 mg/dL. Because hemoglobin A_{1c} represents an average of plasma blood glucose excursions, one must also measure plasma glucose and aim for target levels. The current ADA guidelines recommend that preprandial plasma glucose be in the range of 90 to 130 mg/dL and that postprandial plasma glucose be less than 180.[12]

The preprandial values should be monitored initially, but if a patient reaches the

preprandial goal but not the hemoglobin A_{1c} goal, one should consider monitoring postprandial plasma glucose 2 hours after the start of the meal. It is possible to lower hemoglobin A_{1c} with treatment directed at reducing postprandial plasma glucose values alone,[12,17] eg, with prandial insulin coverage, acarbose, nateglinide, or repaglinide. Whether this approach will prevent microvascular or macrovascular complications has not been studied, however.

Reducing cardiovascular risk factors

Type 2 diabetes, hypertension, and dyslipidemia often coexist and are major risk factors for macrovascular disease.[12] Hence, the ADA recommends modifying cardiovascular risk factors to reduce morbidity and mortality in patients with diabetes.[12]

Blood pressure. Antihypertensive drug therapy, with a target blood pressure lower than 130/80 mm Hg, should be started with agents demonstrated to reduce cardiovascular events in patients with diabetes,[12] ie, thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers (ARBs), and calcium channel blockers. Combinations of two or more drugs are usually needed to achieve the target goal.[18]

Lipids. Recommended target lipid levels are:

- *LDL-C less than 100 mg/dL* (2.6 mmol/L).

Recent data from the Pravastatin or Atorvastatin and Infection Therapy (PROVE-IT)[19] and A to Z trials[20] have been used to suggest that LDL-C goals for patients with known cardiovascular disease should be lowered to less than 70 mg/dL.

PROVE-IT[19] randomized 4,162 patients with acute coronary syndrome, 17.6% of whom had diabetes mellitus, to receive either pravastatin 40 mg or atorvastatin 80 mg daily. LDL-C was lowered from a mean of 106 mg/dL in both groups to 95 mg/dL in the pravastatin group compared with 62 mg/dL in the atorvastatin group. The atorvastatin group had a 16% relative risk reduction in the composite end point of death, myocardial infarction, revascularization procedure, or stroke.

Similarly, in the A to Z trial,[20] randomization of patients with acute coronary syndrome to early vs late therapy with simvastatin conferred a trend toward improved composite cardiovascular outcomes, but this result did not reach statistical significance.

Additionally, the Treating to New Targets (TNT) trial,[21] which randomized 10,003 patients with LDL-C levels lower than 130 mg/dL and stable coronary heart disease to receive either atorvastatin 10 mg or atorvastatin 80 mg, demonstrated LDL-C lowering to 77 mg/dL in the atorvastatin 80 mg group, compared with 101 mg/dL in the 10-mg group. The group receiving 80-mg showed a 22% relative risk reduction in the composite end point of cardiovascular death, nonfatal myocardial infarction, fatal or nonfatal stroke, and resuscitation after cardiac arrest.

The compilation of these data has resulted in ADA recommendations to consider an LDL-C goal of less than 70 mg/dL in high-risk patients with overt cardiovascular disease.

- *Triglycerides less than 150 mg/dL* (1.7 mmol/L)
- *High-density lipoprotein cholesterol greater than 40 mg/dL* (1.1 mmol/L).[12]

Patients who do not achieve these lipid goals with lifestyle modifications such as diet, exercise, and smoking cessation if necessary (smoking cessation raises HDL-C) should start drug therapy; reductions in LDL-C with statin therapy have been shown to reduce the risk of cardiovascular events.[12] For diabetic patients older than 40 years who have a total cholesterol concentration of 135 mg/dL or higher, LDL-C reductions of approximately 30% may be appropriate, regardless of baseline LDL-C levels.[12]

Aspirin 75 to 162 mg/day can be used as secondary prevention in patients with a history of coronary artery disease or other vascular disease (ie, myocardial infarction, vascular bypass procedure, stroke, transient ischemic attacks, peripheral vascular disease, claudication, or angina) and as primary prevention in patients at high cardiovascular risk, including patients older than 40 years or who have additional risk factors (ie, a family history of cardiovascular disease, hypertension, smoking, dyslipidemia, or albuminuria).[12]

Care of hospitalized type 2 diabetic patients

Numerous recent studies suggest that stringent glycemic control in the hospital improves

ACCORD is testing a goal hemoglobin A1c < 6%, systolic pressure < 120 mm Hg, and LDL-C 40–100 mg/dL

patient outcomes, including reducing wound infections and mortality.[12,22–25] Current guidelines from the American College of Endocrinology[26] call for preprandial blood glucose levels of less than 110 mg/dL for all hospitalized patients. The postprandial blood glucose goal for critically ill patients is less than 110 mg/dL and less than 180 mg/dL for noncritical care patients.

Intravenous (IV) insulin infusion is the treatment of choice for critically ill patients and surgical patients in the perioperative and immediate postoperative period.[22–24,27]

IV insulin should not be started unless trained personnel are in attendance, however. The ADA guidelines[12] state that hospitalized patients should be treated by a physician with expertise in the management of diabetes. Glucose should be monitored at least hourly at the bedside.

Several protocols for IV insulin therapy have been developed.[24,28] Regular insulin is typically used for IV infusion; ultra-short-acting insulins are occasionally used, but their IV use has not been well studied. A typical initial infusion rate in perioperative patients is 0.025 units/kg/hour. However, insulin infusion rates may differ substantially, owing to varying levels of insulin resistance related to underlying pathophysiology or current stressors.

The regimen can be changed to subcutaneous insulin when appropriate. When changing to subcutaneous insulin, the first injected dose must be given 1 hour before stopping the insulin infusion because IV insulin is rapidly degraded.

BARRIERS TO CONTROL

Despite the publication of specific evidence-based guidelines, only 37% of adults with diabetes in the United States are achieving target hemoglobin A_{1c} levels of less than 7.0%.[29] Moreover, only 7.3% of adults with diabetes achieve simultaneous control of plasma glucose, blood pressure, and serum cholesterol.[29] In fact, the third National Health and Nutrition Examination Survey (NHANES III) (1988–1994) and NHANES 1999–2000 revealed that although treatment regimens had changed over recent years, glycemic control rates had actually declined.[30]

Several reasons have been proposed for the failure to attain glycemic control in most patients.

Grant et al[31] cited clinical inertia as the reason for the low rate of starting or intensifying pharmacotherapy in patients with type 2 diabetes who are above goal levels for glycemia, blood pressure, and cholesterol. Inertia on the part of the physician may reflect competing demands during brief office visits, avoidance of complex regimens, or reluctance to prescribe additional medications for patients who have demonstrated noncompliance with current regimens.

Negative attitudes toward insulin therapy on the part of both physician and patient may also prevent patients from starting insulin therapy when oral therapies fail to maintain glycemic control or from adhering to it when it is prescribed.[32] Physicians may directly or indirectly communicate negative messages to patients about insulin therapy and imply it is dangerous or a sign of failure to comply with earlier treatment.[32] In addition, patients may be under the mistaken impression that insulin therapy causes the complications of diabetes, having known people on insulin therapy who experienced these outcomes.[32] As a result, patients may refuse to use insulin, or take it only after a recent high glucose reading or after inappropriate consumption of food.[32,33] Moreover, unstable glucose control increases the risk of hypoglycemic unawareness, which is a more dangerous problem.[34]

Only 7.3% of adults with diabetes have their glucose, cholesterol, and blood pressure all under control

STRATEGIES FOR ACHIEVING BETTER GLYCEMIC CONTROL

Better physician-patient communication

The first step in effective glycemic control is an active dialogue between the clinician and the patient.[32] An open, ongoing discussion of patients' concerns can provide many opportunities to correct misperceptions that may pose barriers to adherence to therapy.[32] Adequate diabetes education that includes discussion of the risks and recognition of hypoglycemia and its appropriate therapy can help to allay patients' fears of insulin use.

Physicians must take care not to give the impression that insulin use is a punishment or constitutes failure on the patient's part.[32] It

TABLE 3

Time courses of action for insulin preparations

	ONSET OF GLUCOSE-LOWERING ACTION	TIME TO PEAK GLUCOSE-LOWERING ACTION	DURATION OF ACTION
Basal insulins			
Intermediate-acting			
Neutral protamine Hagedorn (NPH)	1–3 hours	6–8 hours	12–20 hours
Lente			
Long-acting			
Ultralente	2–4 hours	8–12 hours	18–28 hours
Glargine (analog)	1–2 hours	No pronounced peak	About 24 hours
Mealtime (prandial) insulins			
Short-acting			
Regular	30–60 minutes	2–5 hours	5–8 hours
Rapid-acting			
Lispro, aspart, glulisine	5–15 minutes	1 hour	3–5 hours

ADAPTED FROM AHMAN AJ, RIDDLE MC. INSULIN THERAPY IN TYPE 2 DIABETES MELLITUS. IN: LEAHY JL, CEFALU WT, EDITORS. INSULIN THERAPY. NEW YORK: MARCEL DEKKER, 2002: 113–125.

may help to tell patients early on that insulin is a useful tool that may need to be added to their therapy.[32,35]

Do not imply that starting insulin represents a personal failure for the patient

Use of optimal therapies

Many patients with type 2 diabetes will need to use insulin to achieve glycemic goals.

Basal/prandial insulin therapy, ie, using a long-acting insulin for interprandial (basal) coverage plus a short-acting or rapid-acting insulin for mealtime (prandial) coverage, is a physiologic approach to insulin replacement that can be adapted to the individual needs of patients. Many patients with type 2 diabetes start by adding basal insulin, and add prandial insulin later if needed (see below).

The ideal basal insulin should provide consistent interprandial insulin release characteristic of normal subjects, meet 24-hour insulin requirements with one daily dose, have no pronounced peak activity, and cause little or no hypoglycemia.[36,37] The ideal short-acting insulin should mimic the normal insulin secretory response to a meal: rapid onset of action, peak action corresponding to peak nutrient absorption, and short duration of action.

New recombinant (ie, genetically engineered) human insulin analogs possess improved pharmacokinetic characteristics that nearly match normal physiologic time-action insulin profiles.[38] TABLE 3 summarizes the time-action profiles of available insulin preparations.

Insulin glargine (Lantus), a new long-acting insulin analog, was developed in response to the need for better basal insulin coverage.[38]

Insulin glargine forms a microprecipitate that slowly dissolves after injection, providing a uniform rate of delivery over 24 hours.[36,38] This property confers a time-action profile that is very similar to normal basal pancreatic secretion.

The benefits of therapy with insulin glargine have been established in several clinical trials.

In one study, patients with type 2 diabetes continued to take the drugs they had been taking before the study and additionally received either glargine or neutral protamine Hagedorn (NPH) insulin once daily at bedtime, titrated by means of a simple algorithm that targeted fasting plasma glucose levels of 100 mg/dL (5.6 mmol/L).[39] Both therapies achieved target values in most patients at week 24, but patients receiving insulin glargine experienced less daytime and nocturnal hypoglycemia.[39]

Similarly, Yki-Järvinen and colleagues[40] reported lower after-dinner glucose levels and less nocturnal hypoglycemia with insulin glargine than with NPH insulin in a 1-year study in patients with type 2 diabetes.

In a study in adolescent patients with type 1 diabetes,[41] insulin glargine used in combination with preprandial insulin lispro was at least as effective as NPH insulin plus preprandial regular human insulin and was associated with a lower incidence of nocturnal hypoglycemia.

The lower risk of hypoglycemia with glargine than with NPH insulin may reduce a leading barrier to starting insulin therapy in patients with type 2 diabetes mellitus, ie, fear of hypoglycemia.[39]

New rapid-acting insulins. Insulin lispro (Humalog) was the first rapid-acting insulin analog to be available.[42] Subsequently, a mixture called neutral protamine lispro was developed that contains insulin lispro and an intermediate-acting suspension of insulin lispro-protamine crystals. This mixture has shown evidence of postprandial glycemic control superior to that of a mixture containing NPH insulin and regular human insulin.[43]

Insulin aspart (NovoLog), another rapid-acting insulin analog, has absorption characteristics similar to those of insulin lispro.[38]

Insulin glulisine (Apidra), a third rapid-acting insulin analog, has been approved by the US Food and Drug Administration and will be available in 2005.

Practical guidelines for starting insulin therapy

In patients with type 2 diabetes, insulin is most often added to a regimen of one or more oral agents. In this situation, it is best to start with once-daily doses of a basal insulin (NPH or glargine) between 10:00 PM and midnight. (Actually, glargine can be given at any time, but must be given at the same time each day.) When NPH insulin or insulin glargine is added to a sulfonylurea and metformin, the sulfonylurea dose should be decreased to half the maximum dose, even if the patient had been taking larger doses than this.[44]

Although there are a number of methods to determine the initial dose of basal insulin, a weight-based approach (ie, 0.1 units/kg/day) may be best. For lean patients, a typical basal insulin dose is 5 to 10 units. Obese patients are more insulin-resistant and can begin with 10 to 15 units.[45]

TABLE 4

Forced weekly insulin titration schedule for type 2 diabetes

Start with basal insulin 10 U/day at bedtime and adjust weekly

MEAN OF SELF-MONITORED FASTING PLASMA GLUCOSE VALUES FROM PRECEDING 2 DAYS	INCREASE IN INSULIN DOSAGE (U/DAY)
≥ 180 mg/dL (10 mmol/L)	8
140–180 mg/dL (7.8–10.0 mmol/L)	6
120–140 mg/dL (6.7–7.8 mmol/L)	4
100–120 mg/dL (5.6–6.7 mmol/L)	2

Treat to target fasting plasma glucose ≤ 100 mg/dL

Do not increase the dosage if plasma glucose was < 72 mg/dL at any time during the preceding week.

Decrease insulin dose 2 to 4 U/day per adjustment if severe hypoglycemia (ie, hypoglycemia requiring assistance) occurred or plasma glucose was < 56 mg/dL during the preceding week.

A study that compared the effects of insulin glargine and NPH insulin when added to oral therapy in patients with type 2 diabetes used a forced weekly titration schedule (**TABLE 4**) to achieve a fasting glucose level of 100 mg/dL (5.6 mmol/L) or less—an ambitiously low target.[39] Fifty-eight percent of patients receiving insulin glargine achieved a hemoglobin A_{1c} level of 7.0% or less, as did 57.3% of those receiving NPH insulin. Both agents also had similar effects on fasting plasma glucose levels. Further, the patient compliance rate was greater than 90% with each of the two regimens, suggesting the algorithm's ease of application.

However, 25% more patients receiving insulin glargine than NPH reached target hemoglobin A_{1c} and fasting plasma glucose levels without a single instance of documented nocturnal hypoglycemia (defined as a glucose level of ≤ 72 mg/dL [4.0 mmol/L]). The overall rate of hypoglycemia was 21% to 48% lower in the insulin glargine group than in the NPH group.

When adding NPH or glargine to a sulfonylurea and metformin, reduce the sulfonylurea to 1/2 the maximum dose

The findings from this study may serve as the basis for a simple, standardized method to start basal insulin therapy in clinical practice for patients with type 2 diabetes.[39]

Once fasting glucose levels are consistently within a desirable range, glucose levels should be monitored before lunch and dinner and at bedtime to determine the efficacy of oral agents in maintaining euglycemia and the need for additional insulin therapy.[45] Based on the results of this monitoring, combination therapy can be adjusted to address problems at identified times throughout the day.[45] If daytime glucose levels become too low, the dose of oral agents should be decreased. If oral agents do not maintain postprandial glycemic control, different oral agents can be used or consideration can be given to adding short-acting or rapid-acting insulin with the appropriate meal or meals.[45]

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