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Is your patient on target? Optimizing diabetes management

As new evidence emerges and guidelines are frequently revised, optimizing diabetes treatment with an eye toward HbA1c, blood pressure, and lipid goals becomes increasingly complex. Here's help.

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PRACTICE RECOMMENDATIONS

› *Aim for a glycated hemoglobin of <7% for most nonpregnant patients with type 2 diabetes, with a less stringent target for those with severe hypoglycemia, limited life expectancy, advanced micro- or macrovascular complications, and/or extensive comorbidities.* (B)

› *Attempt to treat patients with diabetes and hypertension to a target blood pressure <140/90 mm Hg.* (B)

› *Prescribe statin therapy regardless of baseline lipid levels for all patients who have diabetes and are between the ages of 40 and 75 years.* (A)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence
(B) Inconsistent or limited-quality patient-oriented evidence
(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

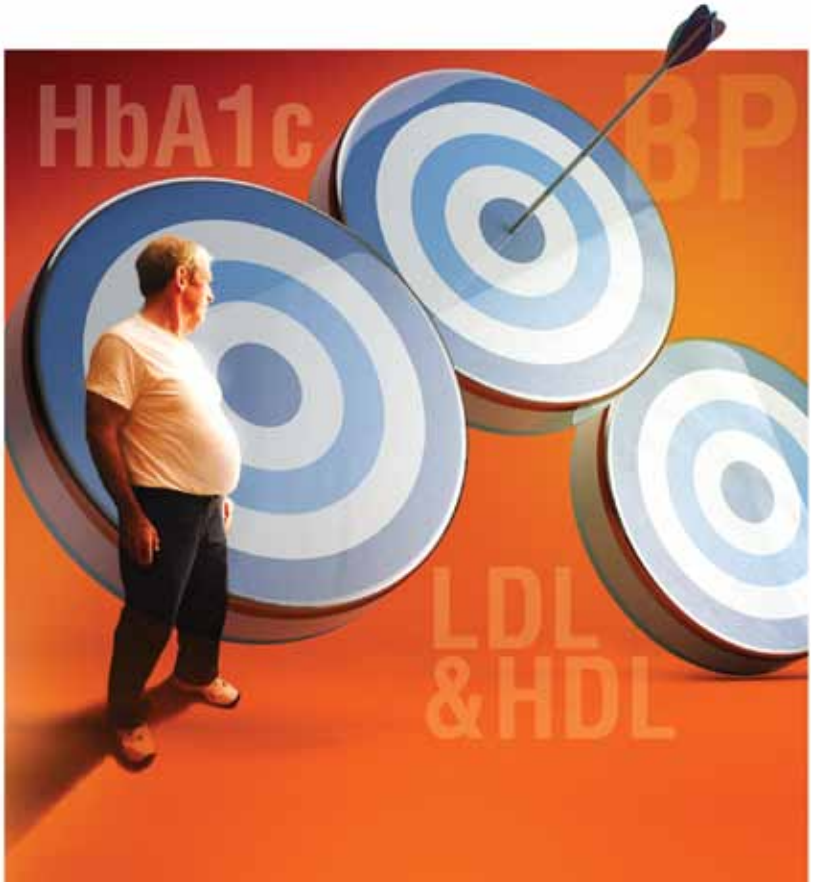
CASE ▶ Dennis D, age 63, was recently diagnosed with diabetes. His glycated hemoglobin (HbA1c) is 7.8%, his blood pressure (BP) is mildly elevated (145/95 mm Hg), and his body mass index (BMI) is 28.5, but his low-density lipoprotein (LDL) cholesterol is 100 mg/dL, his high-density lipoprotein (HDL) cholesterol is 52 mg/dL, and he has no history of cardiovascular disease (CVD). After an unsuccessful attempt to treat him with lifestyle modification, it is time to initiate diabetes therapy.

Other than an alpha-blocker for benign prostatic hyperplasia and a prostaglandin for glaucoma, Mr. D takes no other medications. You prescribe metformin 500 mg twice daily and consider what else to add to keep his diabetes well controlled. Should you prescribe an antihypertensive? And, despite the patient's normal lipid levels, should he begin taking a statin?

Type 2 diabetes has been extensively studied in rigorous randomized controlled trials (RCTs). While studies have provided ample evidence in support of optimal treatment, differing interpretations of the findings are reflected in consensus guidelines developed by expert panels that don't always see eye to eye on what diabetes treatment targets should be and how best to prevent micro- and macrovascular complications.

What's more, recommendations continue to be updated as new data emerge. In February 2014, the Joint Committee on Prevention, Evaluation, and Treatment of High Blood Pressure (JCN 8) revised its target for patients with diabetes to <140/90 mm Hg (from <130/80 mm Hg).[1] This is likely to lead to revisions in other leading consensus guidelines, as well.

Thus, primary care physicians managing the care of patients with diabetes face the challenge of using the latest recommendations in a manner that addresses the entire clinical picture, considering each patient's age and overall health



The challenge faced by primary care physicians? Using the latest recommendations in a way that addresses the entire clinical picture, including the patient's age and overall health status, priorities, and preferences.

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status, priorities, and preferences. We developed this evidence-based review and guideline summary with that in mind.

HbA1c target: How low should you go?

The Diabetes Control and Complications Trial (DCCT), published nearly 20 years ago, studied patients with type 1 diabetes, and found that intensive insulin therapy (HbA1c ≤6%) delayed the onset of retinopathy, nephropathy, and neuropathy.[2] However, there was an important adverse effect of such intensive therapy: Patients in this group suffered from severe hypoglycemic episodes 3 times more frequently than those in the usual care group. Nonetheless, the microvascular benefits of intensive control observed in those with type 1 diabetes were thought to be similar for patients with type 2 diabetes.

The United Kingdom Prospective Diabetes Study (UKPDS), published in 1999, was the first major study to investigate targets for glucose control in patients with type 2 diabetes.[3] Participants treated intensively (mean HbA1c goal, 7%) had a 25% reduction in microvascular complications, including the need for retinal photocoagulation, compared with those on standard control (mean HbA1c, 7.9%). There was also a nonsignificant trend toward a reduction in macrovascular complications in the intensive therapy group, but no difference in overall mortality rate.[3]

A 10-year follow-up of the UKPDS showed that while baseline differences in HbA1c between the 2 groups were lost by one year, reductions in microvascular complications continued to occur in the intensive treatment group.[4] Reductions in myocardial infarction (MI) and death emerged over time, a possible legacy effect (ie, the result of intense treatment early in the course of the disease).

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, published in 2008, studied patients at risk for CVD, defined by either a prior history of CVD or ≥2 other cardiovascular risk factors.[5] Participants, all of whom had poorly controlled type 2 diabetes (mean HbA1c, 8.1%), were randomized to either intensive treatment (HbA1c goal, <6%) or standard therapy (HbA1c goal, 7%-7.9%). The study was discontinued after a mean follow-up of 3.5 years, when those in the in-

tensive therapy group were found to have a higher mortality rate.[5]

The rate of nonfatal MI reported by the ACCORD trial was lower in the intensive therapy group, however, and participants in this group also had delayed onset of microalbuminuria.[6] No differences were seen in serum creatinine concentrations, advanced nephropathy, diabetic eye complications, or nonfatal stroke. Five-year follow up confirmed an increased mortality rate in the intensive therapy group,[7] the result of severe hypoglycemia.[8]

The Veterans Affairs Diabetes Trial (VADT) randomized patients with poorly controlled type 2 diabetes to intensive or standard therapy.[9] At 6 months, the intensive therapy group's HbA1c averaged 6.9%, compared with 8.4% for the standard therapy group. Except for a delay in the progression of albuminuria, no significant effects of intensive therapy were found: Rates of other microvascular complications, major cardiovascular events, and death were similar.[9] It should be noted that the VADT involved fewer participants and shorter follow-up than the other trials cited (**TABLE 1**),[3-10] which may have affected its findings.

The Action in Diabetes and Vascular Disease (ADVANCE) trial, which included participants with either a history of major CVD or ≥1 other CVD risk factors, compared an intensive control group (mean HbA1c, 6.5%) with a standard care group (mean HbA1c, 7.3%)—with mixed results.[10] Microalbuminuria occurred less frequently in the intensive therapy group, but hypoglycemia and hospitalization increased. No reduction in death from any cause, in cardiovascular death, or in major macrovascular events was found.

A less stringent HbA1c target (eg, <8%) may be more appropriate for patients with a higher risk of adverse effects.

How to proceed?

What the experts recommend

In updated standards for the medical care of diabetes released in January 2013,[11] the American Diabetes Association (ADA) calls for an HbA1c goal <7% for most nonpregnant adults with type 2 diabetes. This is in line with the 2012 International Diabetes Federation (IDF) guideline.[12]

The 2011 guideline from the American Association of Clinical Endocrinologists (AACE),[13] however, recommends tighter control—an HbA1c of ≤6.5% for most patients. For patients with diabetes of short duration, a long life expectancy, and no significant history of CVD, the AACE believes that this more aggressive goal has the potential to further reduce the risk of microvascular complications.

A less stringent target (eg, <8%) may be more appropriate for patients with a higher risk of adverse effects. That would apply to those with a history of severe hypoglycemia, a limited life expectancy, advanced micro- or macrovascular complications, or extensive comorbid conditions, as well as to any patient for whom stricter control is difficult to attain even with intensive therapy.[13]

Setting a BP target

In 2003, the 7th report of the Joint Committee on Prevention, Evaluation, and Treatment of High Blood Pressure (JCN 7) recommended a target BP <130/80 mm Hg for diabetes patients.[14] Most major diabetes guidelines, including those of the AACE[13] and IDF,[12] echoed this recommendation. As noted earlier, JNC 8, published earlier this year, loosened the recommendation to <140/90 mm Hg.[1] Although evidence has shown that treatment to a systolic BP <150 mm Hg improves cardiovascular and cerebrovascular outcomes for patients with diabetes,[15] no RCTs have addressed whether more intensive treatment to achieve a systolic BP <140 mm Hg provides further benefit.

The BP of participants in the UKPDS has been examined, with patients with tighter control (<150/85 mm Hg) compared with those with less stringent control (<180/105 mm Hg). The tight control group showed a significant reduction in both death and complications related to diabetes, progression of diabetic retinopathy, and deterioration in visual acuity.[15] Further investigation found that each 10 mm Hg reduction in systolic pressure was associated with a risk reduction of 15% for death related to diabetes, 12% for diabetes-related complications, 11% for MI, and 13% for microvascular complications.[16]

The ACCORD trial randomized participants to more intensive control (systolic BP <120 mm Hg, with a mean of 119.3) or

TABLE 1

HbA1c targets: A summary of the evidence[3-10]

Study (date)	Participants (N)	Intervention	Findings
UKPDS[3] (1977-1991; trial ended in 1997)	25-65 yo with newly diagnosed diabetes (4209)	Intensive therapy (target fasting glucose <6 mmol/L, mean HbA1c, 7.0%) vs standard therapy (target fasting glucose <15 mmol/L, mean HbA1c, 7.9%); patients treated to target with sulfonylurea/insulin or metformin if overweight	Intensive therapy led to: • 12% RRR in any diabetes-related endpoint (*P*=.029) • 10% RRR in diabetes-related death (*P*=.34) • 6% RRR in all-cause mortality (*P*=.44) • 25% RRR in microvascular endpoints, including retinal photocoagulation
UKPDS 10-year follow-up[4] (published in 2008)	Mean age 62 (±8 y) (3277)		Difference in HbA1c converged in 1 y: • 9% RRR in any diabetes-related endpoint (*P*=.04) • 24% RRR in microvascular disease (*P*=.001) • 15% RRR in MI (*P*=.01) • 13% RRR in death from any cause (*P*=.007)
ACCORD[5-8] (2001-2005)*	HbA1c >7.5%, with history of CVD or ≥2 cardiovascular risk factors Mean age 62 (±7 y) (11,140)	Intensive therapy (HbA1c target <6.0%) vs standard therapy (HbA1c target 7%-7.9%)	Increase in mortality in intensive therapy group resulted in premature termination. No reduction in major cardiovascular events. Delayed onset of microalbuminuria in intensive therapy group, but no difference in creatinine level or advanced nephropathy.
VADT[9] (2000-2003; trial ended in 2008)	HbA1c >7.5% Mean age 60 (±9 y) (1791)	Intensive therapy, (HbA1c reduction of 1.5%; mean 6.9%) vs standard therapy (HbA1C <9%; mean 8.4%)	No reduction in cardiovascular outcome or death from any cause in intensive therapy group, but increase in hypoglycemic events in intensive group.
ADVANCE[10] (2001-2003; trial ended in 2008)	History of major CVD or ≥1 other CVD risk (11,140)	Intensive therapy HbA1c <6.5% (mean 6.5%) vs standard therapy based on local guidelines (mean 7.3%)	No reduction in death from any cause, cardiovascular death, or major macrovascular events. Intensive therapy associated with increase in hypoglycemic events and hospitalization but significant reduction in microvascular events (*P*=.01).

ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease; CVD, cardiovascular disease; HbA1c, glycated hemoglobin; MI, myocardial infarction; RRR, relative risk reduction; UKPDS, United Kingdom Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.

* ACCORD glucose control study terminated prematurely in 2008.

standard therapy (systolic BP <140 mm Hg, mean 133.).[17] After 4.7 years, no difference was found in the rates of MI, stroke, or death. However, a significant *increase* in the rate of serious adverse effects from antihypertensive treatment (including hypotension, syncope,

TABLE 2

Blood pressure targets: What the studies show[15-18]

Study (date)	Participants (N)	Intervention	Findings
UKPDS 38[15] (published in 1998)	Analysis of participants in UKPDS trial	Tight control (<150/85 mm Hg) vs less stringent control (<180/105 mm Hg)	Tight control: • 24% RRR in all diabetes endpoints • 32% RRR in death from diabetes • 44% RRR in stroke • 37% RRR in microvascular disease • 56% RRR in heart failure
UKPDS 36[16] (published in 2000)	Prospective observational study of participants in UKPDS		Each 10 mm Hg decrease in mean systolic BP resulted in: • 12% RRR for any diabetic complication • 15% RRR in death from diabetes • 11% RRR in MI • 13% RRR in microvascular complications
ACCORD Study Group[17] (published in 2010)	Participants in ACCORD trial (4733)	Intensive therapy (systolic BP <120 mm Hg) vs standard therapy (systolic BP <140 mm Hg)	No difference in rates of primary outcomes, death from all causes, or stroke; increase in rate of adverse effects from antihypertensive treatment in intensive therapy group (*P*=.001)
INVEST[18] (1997-2000; follow-up 2003 and 2008)	Subgroup analysis of participants with type 2 diabetes (6400)	Tight control (systolic BP <130), usual control (130 to <140) or uncontrolled (≥140)	Cardiovascular event rate of 19.8% in uncontrolled group, 12.6% in usual control group, 12.7% in tight control group

ACCORD, Action to Control Cardiovascular Risk in Diabetes; BP, blood pressure; INVEST, International Verapamil SR-Trandolapril Study; MI, myocardial infarction; RRR, relative risk reduction; UKPDS, United Kingdom Prospective Diabetes Study.

bradycardia, hypokalemia, angioedema, and renal failure) occurred in the intensive control group.[17]

A subgroup analysis of patients with type 2 diabetes enrolled in the International Verapamil SR-Trandolapril Study (INVEST) evaluated systolic BP control and cardiovascular outcomes in those with preexisting coronary artery disease.[18] Participants were categorized as having tight control if their systolic BP <130 mm Hg; usual control, if systolic pressure was between 130 and <140 mm Hg; and uncontrolled, if systolic BP ≥140 mm Hg. Those in the usual control group had lower risks of death, nonfatal MI, and stroke compared with those in the uncontrolled group, but little difference was found between patients in the usual control and tight control groups. The studies are summarized in **TABLE 2**.[15-18]

Interpreting the results: The experts disagree

The ADA recommends that patients with diabetes and hypertension be treated to a goal <140 mm Hg systolic and <80 mm Hg diastolic pressure[11]—more lenient than the recommendations of either the AACE or the IDF. It is not clear whether these recommendations will change, however, given the recent JNC 8 report.[1] A lower systolic target may be appropriate for certain patients, if it can be achieved without undue adverse effects from antihypertensive medication. Older patients

in particular may be at risk for orthostasis or falls as a result of more aggressive treatment.

CASE ▶ Mr. D's most recent BP is 145/95. Given that his goal is <140/90, you elect to start lisinopril 10 mg daily, advise him to monitor his BP at home, and refer him to a dietician to discuss the Dietary Approaches to Stop Hypertension diet.

Lipid levels: When to add statin therapy

Like glucose and BP control, lipid control and, concomitantly, the benefit of statin therapy for patients with type 2 diabetes has been studied extensively (**TABLE 3**).[19-24]

The Scandinavian Simvastatin Survival Study (4S) recruited participants with a history of MI or angina, and included a small diabetes subgroup.[19] Participants were randomized to simvastatin 20 mg daily, with blinded titration up to 40 mg/d, or placebo. Among those with diabetes, patients on simvastatin had a 55% reduction in risk for major coronary heart disease events and a 43% reduction in total mortality. The risk reduction did not depend on baseline levels of total cholesterol, LDL cholesterol, HDL cholesterol, or triglycerides.

Cholesterol and Recurrent Events (CARE), which studied participants with a history of MI 3 to 20 months prior to the start of the study and also included a diabetes subgroup, had a similar outcome.[20] Compared with placebo, treatment with pravastatin 40 mg/d reduced the risk of both coronary events and revascularization procedures by 25%.

The Heart Protection Study randomized patients with either diabetes or a history of occlusive arterial disease to receive simvastatin 40 mg daily or placebo.[21] In the treatment group, the risk of major vascular events was reduced in patients with diabetes by 27%. Improvements were seen in patients with LDL cholesterol levels both above and below 116 mg/dL.

Multiple studies have evaluated the benefits of atorvastatin for patients with diabetes. All have demonstrated a significant reduction in the risk of MI and death in those on statin therapy. The Treating to New Targets study showed a 25% reduction in major cardiovascular events in those treated with 80 mg atorvastatin daily (mean LDL, 77 mg/dL) vs those treated with 10 mg of the drug (mean LDL, 86 mg/dL).[22] The Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm (ASCOT-LLA)[23] and the Collaborative Atorvastatin Diabetes Study (CARDS)[24] were both terminated early due to the magnitude of benefit seen with statin therapy. In contrast to LDL, evidence for non-LDL treatment goals is lacking in the diabetes literature. Also, there is little evidence to support nonstatin cholesterol-lowering therapy for the management of diabetes patients.

The updated standards released by the ADA in January 2013 recommend statin therapy, regardless of LDL level, for patients who have diabetes and known CVD.

Statin use is widely recommended

In 2008, the ADA and the American College of Cardiology Foundation (ACCF) produced a joint consensus statement regarding lipoprotein management for patients with diabetes and multiple CVD risk factors.[25] Target LDL was recommended at <100 mg/dL for moderately high-risk primary prevention patients, including those with diabetes. For patients with diabetes and ≥1 other risk factors, the ADA/ACCF recommended an LDL goal <70 mg/dL. The 2011 AACE guideline has the same treatment goals,[13] while the 2012 IDF guidelines are more aggressive.[12] For primary prevention, the AACE endorses an LDL goal <80 mg/dL, and <70 mg/dL for those with known CVD.[13]

The updated standards released by the ADA in January 2013 recommend statin therapy regardless of LDL level for patients who have diabetes and known CVD, as well as for those ages 40 years and older who do not have CVD but have ≥1 other risk factors. Specific risk factors include hypertension, dyslipidemia, albuminuria, and a family history of CVD.[11]

The latest statin guideline. In November 2013, the American College of Cardiology and American Heart Association (ACC/AHA) published a new guideline for the treatment of cholesterol to reduce cardiovascular risk,[26] but said nothing for or against specific LDL or non-HDL cholesterol targets. The ACC/AHA recommends that all patients who have diabetes and are between the ages of 40 and 75 years be treated with a moderate dose

TABLE 3

Cholesterol treatment for patients with diabetes: A look at the evidence[19-24]

Study (date)	Participants (N)	Intervention	Findings
SSSS (4S)[19] (1988-1989; trial ended in 1994)	Diabetes subgroup Mean age 60 (±7 y) History of MI or angina Total cholesterol 5.5-8.0 mmol/L (202)	Simvastatin 20-40 mg/d vs placebo	Simvastatin group: • relative risk=.57 for total mortality (*P*=.087) • relative risk=.45 for major CHD events (*P*=.002) • relative risk=.63 for any atherosclerotic event (*P*=.018)
CARE[20] (1989-1991; trial ended in 1996)	Diabetes subgroup Mean age 61 (±8 y) History of MI 3-20 months before study LDL cholesterol 115-174 mg/dL (586)	Pravastatin 40 mg/d vs placebo	25% RRR in composite of coronary events
HPS[21] (1994-1997; trial ended in 2001)	Diabetes subgroup (included patients with type 1 diabetes) Mean age 62 (±9 y) Total cholesterol >135 mg/dL (5963)	Simvastatin 40 mg/d vs placebo	27% reduction in major coronary events
TNT[22] (1998-1999; trial ended in 2004)	Diabetes subgroup Mean age 63 (±8 y) History of CHD (1501)	Atorvastatin 80 mg/d vs atorvastatin 10 mg/d	25% reduction in major cardiovascular events for group on higher dose
ASCOT-LLA[23] (1998-2000; trial terminated prematurely in 2002)	Diabetes subgroup Mean age 64 (±8 y) Hypertension ≥3 other risk factors, including diabetes No known CHD (2532)	Atorvastatin 10 mg/d vs placebo	23% reduction in major cardiovascular events and procedures (*P*=.30) Subgroup analysis underpowered due to trial termination
CARDS[24] (1997-2001; trial terminated prematurely in 2003)	Mean age 62 (±8 y) ≥1 CV risk factors No known CVD (2838)	Atorvastatin 10 mg/d vs placebo	37% reduction in ≥1 major cardiovascular events

ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm; CARDS, Collaborative Atorvastatin Diabetes Study; CARE, Cholesterol and Recurrent Events; CHD, coronary heart disease; CVD, cardiovascular disease; HPS, Heart Protection Study; LDL, low-density lipoprotein; MI, myocardial infarction; RRR, relative risk reduction; SSSS, Scandinavian Simvastatin Survival Study; TNT, Treating to New Targets.

of a statin—a target supported with strong (strength of recommendation: **A**) evidence.

Patients with diabetes and an estimated 10-year risk of CVD >7.5% should be considered for high-intensity statin therapy, according to the ACC/AHA.[26] For patients younger than 40 or older than 75, the decision to initiate statin therapy should be made by weigh-

ing the potential cardiovascular benefits, the risk of adverse effects, and the potential for drug-drug-interactions, as well as patient preference.

CASE ▶ You discuss the need for moderate-dose statin therapy with Mr. D. He is hesitant at first, referring to a coworker who had "leg cramps" when he was taking a statin. You emphasize the importance of prevention in the care of his diabetes and convince the patient to begin a trial of atorvastatin 40 mg daily.

You warn Mr. D of the possibility of an allergic reaction, rash, or cough from lisinopril and loose stools from metformin, and advise him to call if he develops muscle cramps that could be associated with the statin. Finally, you stress the importance of lifestyle modification, including diet and weight loss, and schedule a follow-up visit in 3 months.

At Mr. D's next visit, you will check his HbA1c and BP. If his HbA1c is still >7.0%, you may increase the dose of metformin or add a sulfonylurea. The dose of lisinopril could be increased if the patient's BP continues to be elevated. There will be no need to recheck Mr. D's cholesterol levels, however, because the purpose of the statin therapy is to improve overall outcomes, rather than to achieve a target goal. **JFP**

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The ACC and AHA published a new guideline for the treatment of cholesterol to reduce cardiovascular risk, but said nothing for or against specific LDL or non-HDL cholesterol targets.

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