

ANTIHYPERGLYCAEMIC AGENTS

KEY POINTS

- **Tight glycaemic control (HbA1c <7% or 53mmol/mol) reduces the frequency of microvascular events and this remains appropriate for people who are robust and have sufficient life expectancy to derive benefit.**
- **Glycosylated haemoglobin levels below 6.5% (48mmol/mol) are associated with increased morbidity and mortality in the elderly.**
- **Adverse effects of antidiabetic treatment are more common in elderly people.**
- **Decreasing intensity of treatment after 10 years or more of good glucose control does not seem to result in loss of the microvascular benefits.**
- **Intensity of diabetes management should be reduced in frail elderly patients in order to minimise hypoglycaemia.**

CONTEXT

This guide considers the use of antihyperglycaemics in elderly patients.

RECOMMENDED DEPRESCRIBING STRATEGY

- Patients who have been taking sulphonylureas for more than 10 years are likely to have limited effectiveness of the agent. If diabetes management goals are satisfactory, dose reduction (with appropriate monitoring to ensure lack of effect) with a view to cessation would be reasonable.
- In elderly people taking antihyperglycaemics, who have an HbA1c below 6.5% (48mmol/mol) reduction of treatment, followed by appropriate monitoring would be appropriate.
- Patients who have hypoglycaemia associated with their antihyperglycaemic therapy should have the intensity of treatment reduced.

A detailed antihyperglycaemic deprescribing guide is shown on **Page 5**.

BENEFIT VERSUS HARM

| | Favours Continuing Medication | Favours Deprescribing Medication |
|---|---|--|
| Main Benefits <ul style="list-style-type: none"> ➤ Reduced micro and macro-vascular complications of diabetes | Increased Benefit <ul style="list-style-type: none"> ➤ Troublesome hyperglycemic symptoms (e.g. thirst, polyuria, neuropathy) ➤ Comorbid cardiovascular risk factors | Decreased Benefits <ul style="list-style-type: none"> ➤ Frailty, especially with reduced BMI or poor dietary patterns ➤ Limited life expectancy due to comorbidities (dementia, heart failure, airways disease, malignancy) |
| Main Harms <ul style="list-style-type: none"> ➤ Hypoglycaemia and its consequences | Reduced Harms <ul style="list-style-type: none"> ➤ Relatively young with high BMI | Increased Harms <ul style="list-style-type: none"> ➤ Glycosylated haemoglobin of 6.5% (48mmol/mol) or less ➤ Frailty, increased falls risk |

BACKGROUND

Type 2 diabetes is a chronic disease characterised by deterioration of glycaemic control, most commonly due to loss of pancreatic beta cell mass and functions on a background of insulin resistance (see **Figure 1**).¹

There are multiple proposed causes for beta cell dysfunction in type 2 diabetes over time. Factors such as consistent hyperglycaemia, obesity, hyperlipidaemia and possibly the use of insulin secretagogues such as sulphonylureas and gliptins have been implicated.^{2,3}

When managing diabetes in older people, the presence of comorbidities and frailty are critical to establishing treatment goals.

Tight glycaemic control (HbA1c <7% or 53mmol/mol) reduces the frequency of microvascular events and this remains appropriate for people who are robust and have sufficient life expectancy to derive benefit.

Intensive glycaemic control strategies, however, also increase the frequency of hypoglycaemia, which has been associated with poor outcomes (increased mortality, worsening cardiovascular disease, increased falls, increased accidents) in elderly people. In a retrospective study of patients 50 years and older with diabetes, both low and high HbA1c levels were associated with increased mortality (see **Figure 2**).⁴

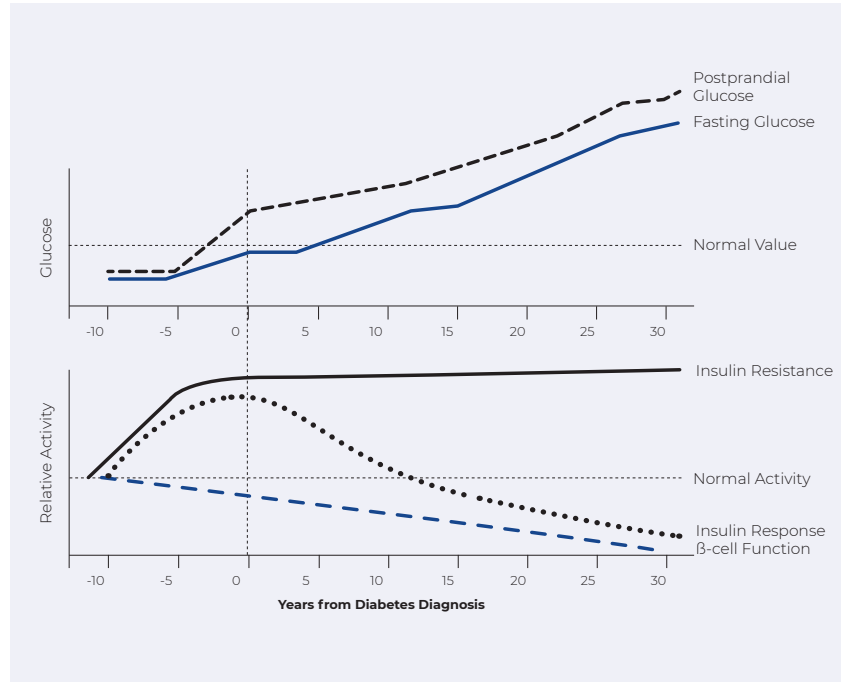


Figure 1: Natural progression of Type 2 diabetes¹

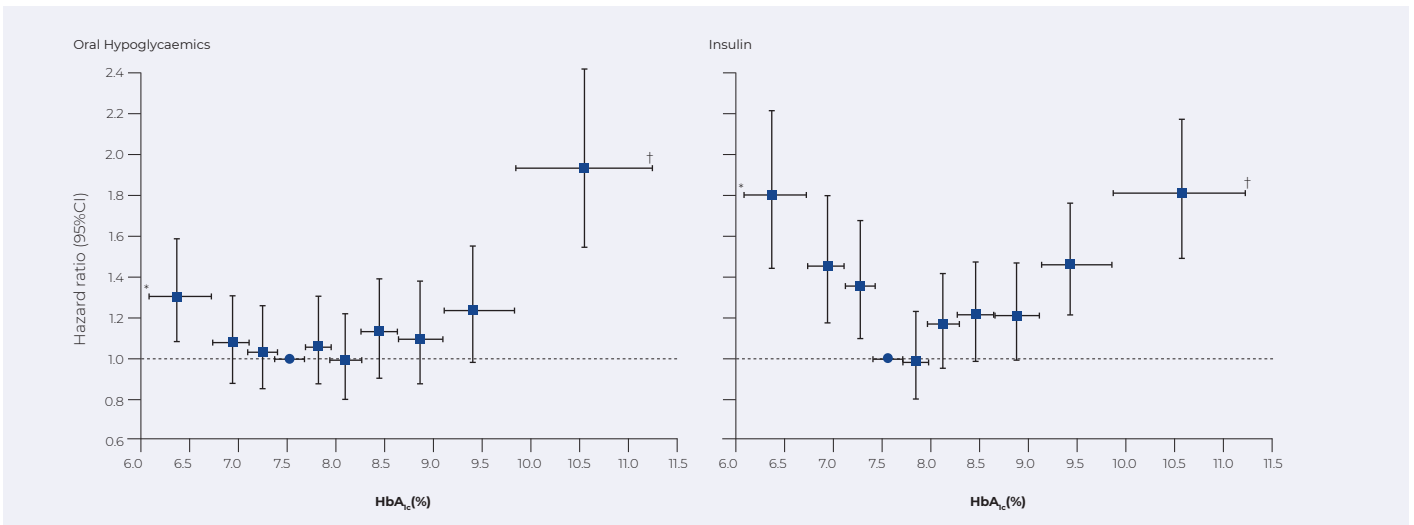


Figure 2: Relationship between HbA1c and mortality for patients taking oral hypoglycaemics or insulin⁴

EFFICACY

The RACGP guidelines for management of diabetes recommend commencing pharmacologic therapy with metformin. Addition of sulphonylureas is widely accepted as the next step in therapy, but the availability of newer, effective oral agents (SGLP2 inhibitors, DPP4 inhibitors and others) has meant that many guidelines now advocate a patient centred approach to the addition of a second agent, with the choice of agent determined by comorbidities and potential impact of adverse effects (e.g. weight gain, fracture risk, risk of hypoglycaemia).⁵

Table 1 shows some of the key features of available treatments for diabetes. In elderly people, avoiding medications which are not recommended in significant renal dysfunction and those that are more likely to cause hypoglycaemia is a reasonable strategy.

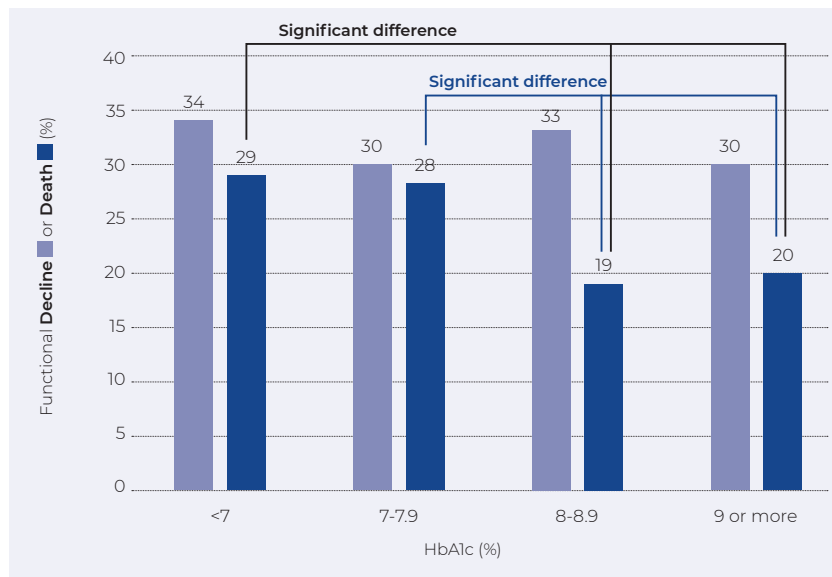


Figure 3: Rate of functional decline or death at 2 years¹⁰

| PHARMACOLOGIC STRATEGY | EFFICACY | CARDIO-VASCULAR BENEFITS | HYPO-GLYCAEMIA RISK | IMPACT ON WEIGHT | MAIN ADVERSE EFFECTS | USE IN RENAL DYSFUNCTION (CR CL < 30ML/MIN) |
|--|--------------|--------------------------|---------------------|------------------|---------------------------|---|
| Metformin | Moderate | Yes | Low | Loss | Gastrointestinal | Avoid |
| Sulphonylureas (glibenclamide, gliclazide) | High | No | High | Gain | Hypoglycaemia | Monitor Closely |
| Glitazones (Pioglitazone, Rosiglitazone) | Moderate | Unclear | Low | Gain | Oedema | Unchanged |
| DPP4 Inhibitors or Gliptins (Alogliptin, Linagliptin, Saxagliptin, Sitagliptin, Vildagliptin) | Low/Moderate | No | Low | Neutral | - | Reduce all except linagliptin |
| SGLT2 inhibitors (Dapagliflozin, Empagliflozin, Ertugliflozin) | Moderate | Yes | Low | Loss | Genital fungal Infections | Avoid |
| GLP1 agonists (Dulaglutide, Exenatide, Liraglutide) | High | Yes | Low | Loss | Gastrointestinal | Caution |
| Insulin | High | Yes | High | Gain | Hypoglycaemia | Unchanged |

Table 1: Features of pharmacologic treatments for Type 2 diabetes

DIABETES MANAGEMENT IN THE ELDERLY

The management of diabetes in elderly patients, often with multiple comorbidities can be complicated. There is a need to incorporate an appreciation of the impact of diabetes treatment on common syndromes and issues in the elderly (e.g. falls, urinary incontinence, sarcopenia).^{6,7} As a result of the significant adverse impacts of intensive glycaemic control in elderly people, a reduction in intensity of management for frailer people is suggested in many guidelines.⁸

In particular, avoidance, or careful monitoring, of the use of insulin and/or sulphonylureas is strongly suggested. A recent evidence-based practice guideline for deprescribing of antihyperglycaemic agents in older persons has been published (see **Figures 4 and 5**).⁹ It is also worth noting that hypoglycaemia caused by sulphonylureas dependent on functioning beta cells. As beta cell function declines with duration of type II diabetes the frequency of hypoglycaemia in some patients on long-term sulphonylureas may be lower.

Given the increasing likelihood of beta cell failure with sulphonylureas and the availability of newer agents, the usage of sulphonylureas in elderly people should be limited. Similarly, although basal/bolus insulin regimens show improved control of glycaemia, changing to less intensive daily or twice daily regimens of insulin reduces risk of hypoglycaemia and the frequency of BSL testing.

In older adults, especially with limited life expectancy, functional decline can be expected to be faster in patients with higher levels of adverse events such as hypoglycaemia. Yau et al examined the functional decline of 185 community based elderly patients (mean age 80 years) with type 2 diabetes who were approved for nursing home care.¹⁰ They determined whether functional decline (based on reduced score on five basic activities of daily living) or death occurred over 6, 12 and 24 months and related this to the HbA1c level. At 2 years, higher HbA1c levels were associated with less functional decline or death (p for trend 0.006) (see **Figure 3**). When they accounted for confounding factors (age, sex, race, baseline function, comorbid conditions, insulin use) **they found that an HbA1c of 8-8.9% was associated with a lower likelihood of death or functional decline than an HbA1c of 7-7.9%.**¹⁰ They suggested that guidelines that recommend a target HbA1c of 8% or less for older adults with limited life expectancy may be lower than necessary to maintain function.

Sussman et al¹¹ examined the rates of “deintensification” of diabetic therapy in patients over 70 years old. They examined the rate of deintensification of treatment used in patients according to their HbA1c, in the categories of very low (<6%, n= 12917), moderately low (6-6.4%, n= 23,769) and not low (>6.5%, n= 143,305). Deintensification rates were 27%, 21% and 17.5% respectively.¹¹

Life expectancy was estimated using the patient’s age and their Charlson-Deyo score. Patients with less than 5 years of life expectancy had a 21.3% chance of diabetic therapy deintensification, those with 5 to 10 years had a 18.5% chance, and those with more than 10 years had a 17.2% chance. The authors indicated that **current guidelines for management of diabetes focus on preventing underuse rather than overuse** and concluded “Until guidelines and performance measures specifically call for deintensification for patients who are at risk for being harmed by overtreatment, (deintensification) rates are likely to remain low”.¹¹

Taken together, these studies indicate that there comes a time in treatment of diabetes when the risks of treatment are not balanced by the benefits of glycaemic control. Treating to a lower glycosylated haemoglobin of 7% (53mmol/mol) vs 8% (64mmol/mol) does not increase death or macrovascular events over 10 years, but can decrease harm (hypoglycaemia), especially in older people with comorbidities.

IS THERE A “LEGACY EFFECT” OF GOOD GLYCAEMIC CONTROL?

The United Kingdom Diabetes Prevention Study (UKPDS) studied intensive control compared to less intensive control of glycaemia in type 2 diabetes for a period of 10 years.¹² They found a reduction in microvascular complications and the results of this study have guided treatment for the last two decades. A 10 year followup of survivors of the study showed interesting results implicating a legacy effect of good glycaemic control.

At the completion of the 10 year intensive treatment options (either sulphonylurea/insulin or metformin) patients returned to “usual care” and were monitored for outcomes for a further 10 years.¹³ Although the glycosylated haemoglobin levels of patients in the intensive treatment arms rapidly returned to those in the usual treatment arms, the rate of microvascular complications in the patient who has previously had intensive treatment remained lower for an average followup of 7.7 years. The authors conclude that there is “...a sustained legacy effect of an intensive glucose control strategy that appears to be longer than previously reported.”¹⁰

The implication of these results is that decreasing the intensity of control of glucose levels later in the course of type 2 diabetes may not adversely impact on clinical outcomes.



ADVERSE EFFECTS

The main adverse effects of antihyperglycaemic agents are shown in **Table 1**. As expected, the adverse effect of most concern is hypoglycaemia.

The elderly are more likely to suffer serious adverse consequences as a result of hypoglycaemia, and there are differences in recognising hypoglycaemia in older people. Symptoms are often non-specific or atypical (often confusion or a passive delirium) and can be misinterpreted or misdiagnosed.¹⁴

Hypoglycaemia from sulphonylureas is dependent on functioning beta cells, and as a result, the frequency of hypoglycaemia in patients on long term sulphonylureas may reduce.



FACTORS TO CONSIDER

IN FAVOUR OF DEPRESCRIBING

- ✔ Long duration of therapy with sulphonylureas is associated with a reduction in efficacy, most likely due to beta cell failure. In patients achieving an appropriate target HbA1c after long term use (>10 years) it is likely that the impact of the sulphonylurea is minimal and dose reduction or cessation may be possible.

- ✔ In elderly or frail patients, where the intensity of diabetic management can be reduced, reduction of any antidiabetic therapy (especially insulin or sulphonylureas which predispose to hypoglycaemia) may be appropriate.

AGAINST DEPRESCRIBING

- ✘ In people where intensive treatment of diabetes is still likely to have a long term benefit, ongoing management is appropriate.

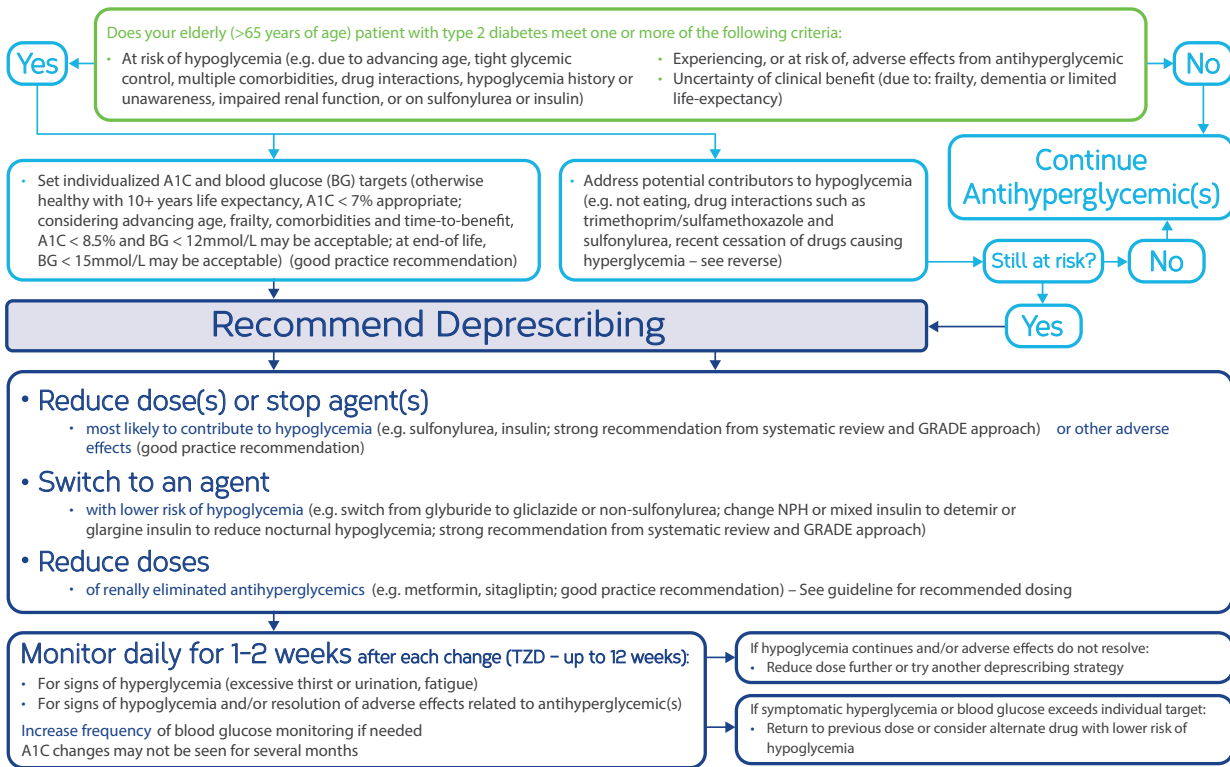


Figure 4: Deprescribing antihyperglycaemic agents (algorithm) in older persons⁹ [glyburide = glibenclamide in Australia]

Antihyperglycemics and Hypoglycemia Risk

| Drug | Causes hypoglycemia? |
|--|--|
| Alpha-glucosidase inhibitor | No |
| Dipeptidyl peptidase-4 (DPP-4) inhibitors | No |
| Glucagon-like peptide-1 (GLP-1) agonists | No |
| Insulin | Yes (highest risk with regular insulin and NPH insulin) |
| Meglitinides | Yes (low risk) |
| Metformin | No |
| Sodium-glucose linked transporter 2 (SGLT2) inhibitors | No |
| Sulfonylureas | Yes (highest risk with glyburide and lower risk with gliclazide) |
| Thiazolidinediones (TZDs) | No |

Drugs affecting glycaemic control

- Drugs reported to cause hyperglycemia (when these drugs stopped, can result in hypoglycemia from antihyperglycemic drugs) e.g. quinolones (especially gatifloxacin), beta-blockers (except carvedilol), thiazides, atypical antipsychotics (especially olanzapine and clozapine), corticosteroids, calcineurin inhibitors (such as cyclosporine, sirolimus, tacrolimus), protease inhibitors
- Drugs that interact with antihyperglycemics (e.g. trimethoprim/sulfamethoxazole with sulfonylureas)
- Drugs reported to cause hypoglycemia (e.g. alcohol, MAOIs, salicylates, quinolones, quinine, beta-blockers, ACEIs, pentamidine)

Engaging patients and caregivers

- Some older adults prefer less intensive therapy, especially if burdensome or increases risk of hypoglycemia
- Patients and/or caregivers may be more likely to engage in discussion about changing targets or considering deprescribing if they understand the rationale:
 - Risks of hypoglycemia and other side effects
 - Risks of tight glucose control (no benefit and possible harm with A1C < 6%)
 - Time to benefit of tight glucose control
 - Reduced certainty about benefit of treatment with frailty, dementia or at end-of-life
- Goals of care: avoid hyperglycemic symptoms (thirst, dehydration, frequency, falls, fatigue, renal insufficiency) and prevent complications (5-10 years of treatment needed)
- Many countries agree on less aggressive treatment of diabetes in older persons
- Reviewing options for deprescribing, as well as the planned process for monitoring and thresholds for returning to previous doses will help engage patients and caregivers

Hypoglycemia information for patients and caregivers

- Older frail adults are at higher risk of hypoglycemia
- There is a greater risk of hypoglycemia with tight control
- Symptoms of hypoglycemia include: sweating, tachycardia, tremor BUT older patients may not typically have these
- Cognitive or physical impairments may limit older patient's ability to respond to hypoglycemia symptoms
- Some drugs can mask the symptoms of hypoglycemia (e.g. beta blockers)
- Harms of hypoglycemia may be severe and include: impaired cognitive and physical function, falls and fractures, seizures, emergency room visits and hospitalizations

Tapering advice

- Set blood glucose & A1C targets, plus thresholds for returning to previous dose, restarting a drug or maintaining a dose
- Develop tapering plan with patient/caregiver (no evidence for one best tapering approach; can stop oral antihyperglycemics, switch drugs, or lower doses gradually e.g. changes every 1-4 weeks, to the minimum dose available prior to discontinuation, or simply deplete patient's supply)
- Doses may be increased or medication restarted any time if blood glucose persists above individual target (12-15 mmol/L) or symptomatic hyperglycemia returns

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Farrell B, Black C, Thompson W, McCarthy L, Rojas-Fernandez C, Lochnan H, et al. Deprescribing antihyperglycemic agents in older persons. Evidence-based clinical practice guideline. *Can Fam Physician* 2017;63:832-43 (Eng), e452-65 (Fr).



Figure 5: Deprescribing antihyperglycaemic agents (notes) in older persons⁹

RESOURCES

- GENERAL INFORMATION
- ALLOPURINOL
- ANTIHYPERGLYCAEMICS
- ANTIHYPERTENSIVES
- ANTIPSYCHOTICS
- ASPIRIN
- BENZODIAZEPINES
- BISPHOSPHONATES
- CHOLINESTERASE INHIBITORS
- GLAUCOMA EYE DROPS
- NSAIDS
- OPIOIDS
- PROTON PUMP INHIBITORS
- STATINS
- VITAMIN D AND CALCIUM

AUTHORSHIP

This guide was updated by Dr Peter Tenni and Dr David Dunbabin from a document developed in consultation with the Deprescribing Reference Group.

DISCONTINUATION SYNDROMES

None described

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