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Prescribing, monitoring, and deprescribing drugs in geriatric DM patients

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1. RECOMMENDATIONS

A. Blood sugar targets in persons aged over 75 should be individualized, taking into account the clinical characteristics of the patient and potential adverse effects of the antidiabetic drug prescribed.
B. The therapeutic target for glycated hemoglobin should be determined for each individual patient, taking into consideration life expectancy and the benefits and risks of improved blood sugar control.
C. Higher glycated hemoglobin targets may be used in situations where the patient needs to use drugs that can cause hypoglycemia (e.g., insulin); in the event that glucose and glycated hemoglobin levels start to approach normal levels, the pharmacological therapy should be reduced to lower the risk of hypoglycemia.
D. Deprescription of antidiabetic drugs should be considered if the patient's glycated hemoglobin level falls below 6.5% (48 mmol/mol), even if the patient has no side effects or the drug is not a medication that causes hypoglycemia.

2. STRENGTH OF THE RECOMMENDATIONS

The quality of the evidence is low. Recommendations are mostly based on best practice and only partially supported by published evidence.

3. SUPPORTING EVIDENCE

See appendix.

4. AREAS OF UNCERTAINTY AND FUTURE PERSPECTIVES

Well-designed observational studies and randomized clinical trials are needed for a better definition of clinical decisions on deprescription in the elderly. Such studies should include adequate numbers of patients with advanced aged and they should be focused on appropriate outcomes, which could differ from those usually considered in younger individuals.

APPENDIX

Geriatric DM patients are heterogeneous in terms of varying ages of disease onset, clinical characteristics, comorbidities [1], pathogenesis,

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and pathophysiology [2]. Available data indicate that increases in post-prandial glycemia contribute more to hyperglycemia in patients over 65 years old than in younger ones [3], suggesting an age-related progressive decline in insulin secretion related to eating [4,5]. Clinical and pathophysiological differences are compounded by differences in the risk of diabetic complications: although the risk of cardiovascular disease progressively increases with increasing age [6], the relative increase in cardiovascular risk is lower in late-onset DM compared to earlier-onset cases [1]. Therefore, pharmacological therapy for DM in geriatric patients needs to be individualized, taking into account the duration and complications of DM, functioning, comorbidities, life expectancy, the presence of a caregiver, and the ability to follow complex treatments [7].

Glycemic control

The aim of DM treatment is to avoid acute and chronic complications. In geriatric patients, the expected benefit of well-controlled glucose for preventing chronic complications is inversely related to life expectancy. In addition, the risk of certain drug-related adverse effects, such as severe hypoglycemia, is higher in geriatric patients, especially those with comorbidities [8]. Cardiovascular diseases account for more than half of deaths in geriatric DM patients as well as many hospitalizations [9], especially in frail patients [10]. On the other hand, given that the risk of major cardiovascular events associated with DM is lower in older than younger adults [11], it may be less beneficial to treat hyperglycemia in older than younger individuals. Data on the long-term effects of improved blood sugar control on cardiovascular risk have mostly focused on patients under 75 years [12,13]; in the ACCORD study, age over 79 was an exclusion criterion [14]. In the ADVANCE study, a sub-group analysis was conducted on patients over 65 years of age, which showed no differences between the intensified treatment arm and the control group, but not for those over 75 years of age [15].

To a large extent, guidelines suggest higher blood-glucose targets for geriatric patients, especially if they have reduced autonomy, frailty, or comorbidities. The American Diabetes Association (ADA) recommends a therapeutic HbA1c target of 7.5% (58 mmol/mol) for relatively healthy geriatric patients, and higher targets (8.0-8.5%, 64-69 mmol/mol or more) for those with severe comorbidities, disability, disability, or reduced life expectancy (7). The American Association of Clinical Endocrinologists (AACE) also suggest a more ambitious target for geriatric patients (below 6.5%/48 mmol/mol, provided it can be safely achieved), while for those with severe comorbidities, a high risk of hypoglycemia, or limited life expectancy a more conservative therapeutic approach is suggested, without HbA1c targets, aiming only to treat symptomatic hyperglycemia [16]. The American College of Physicians (ACP) also do not recommend a specific HbA1c target for patients over 80 years of age, with a life expectancy of less than 10 years, or major comorbidities, but they recognize the need to avoid continued hyperglycemia and severe hypoglycemia in geriatric patients and, thus, propose an optimal HbA1c range rather than a maximum threshold. The ACP guidelines recommend that treatment should be increased in geriatric patients when their HbA1c levels exceed 7-8% (53-64 mmol/mol) and reduced when HbA1c is below 6.5% (48 mmol/mol) [17]. The Italian guidelines recommend a more ambitious target (HbA1c 7%/53 mmol/mol), if this can be achieved without using drugs that could lead to hypoglycemia (i.e., insulin, sulfonylureas, or glinides), without setting a minimum target. However, if insulin or insulin secretagogues are used, HbA1c should be maintained in the range of 7-7.5% (53-58 mmol/mol) in relatively healthy geriatric patients, or 7.5-8% (58-64 mmol/mol) in individuals with frailty, comorbidities, or cognitive decline [18].

Risk of overtreatment and deprescribing

Deprescribing unnecessary drugs in geriatric patients is a strategy that aims to improve quality of care while reducing costs [19]. Current guidelines on the management of DM recommend higher therapeutic targets in geriatric patients, especially those who are frail or have comorbidities [18]; more in general, overtreatment should be avoided in geriatric or frail patients, with an indication to reduce drugs where possible [18,20]. However, there is no clear indication as to when and how to deprescribe drugs. There has been an attempt to create evidence-based guidelines for the deprescription of antidiabetic drugs in geriatric patients [21], but only observational studies with poor methodology are available [22]. A recent systematic review found ten observational studies [23] reporting either deprescription of antidiabetic drugs or therapeutic modifications to prescribe safer drugs [24,25]. Studies carried out on geriatric, frail persons living in long-term care facilities, where drugs were stopped or substantially reduced in patients with good glucose control, showed a reduced risk of hypoglycemia, without HbA1c increasing above age-specified targets [25-27]. In contrast, a retrospective study of geriatric DM patients who were discharged after acute myocardial infarction showed that suspending antihyperglycemic therapy was associated with increased mortality [28]. While the available evidence shows encouraging results in terms of controlling glycemic metabolism, it does not provide any information on possible predictors of metabolic outcomes. This could explain why very few geriatric patients with reduced HbA1c undergo

deprescription [29-31], unless they report hypoglycemia [32] or drug-related adverse effects [21].

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This statement is:	**Quality of the evidence** (in the case of recommendation):
☐ Recommendation (supported by published evidence) ☒ **Best practice** (supported by expert opinion)	☒ **Low** ☐ Moderate ☐ High