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1 **Deprescribing glucose-lowering therapy in older adults with**
2 **diabetes - a systematic review of recommendations**

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32 **TO THE EDITOR,**

33 Overtreatment by glucose-lowering treatment (GLT) is frequent, and may induce harmful
34 hypoglycemic events in older people with type 2 diabetes (T2D), significantly increasing
35 morbi-mortality¹. Avoiding overtreatment by GLT, either by prescribing appropriate GLT
36 according to their individual risks-benefits balance or by deprescribing GLT, is therefore a key
37 issue in the management of older patients, as recommended by various scientific societies these
38 last years². Nevertheless, there is currently no consensus on the definition of GLT overtreatment
39 in older people³, which prevents a clear statement on which patients should undergo
40 deprescribing of GLT. It is therefore worthwhile to define the profiles of patients for whom
41 GLT should be deprescribed. This systematic review of clinical practice guidelines (CPGs)
42 aimed to compare the recommendations defining profiles of older patients in whom
43 deprescribing GLT is recommended.

44

45 **METHODOLOGY**

46 This systematic review included all CPGs focused on older people (≥ 65 years old), related to
47 some aspects of T2D management, providing distinct recommendation(s) addressing the
48 deprescription of GLT, endorsed by scientific societies or expert groups from Europe or North
49 America, and published in English or French from 2015 onward. Literature databases were
50 comprehensively searched (MEDLINE, EMBASE and CINAHL complete) using research
51 equations, as well as websites of CPG repositories or scientific societies of geriatrics or
52 endocrinology. After removing duplicates, we selected eligible CPGs following a two-step
53 strategy ((1) titles-and-abstracts review, (2) full-texts review of the remaining records after step
54 (1)) independently by 2 reviewers. All conflicts were adjudicated by a third reviewer. We assess
55 methodological quality of included CPGs using the AGREE-II score⁴. Finally, we extracted the
56 content of all recommendations defining profiles of patients to be targeted for deprescribing

57 GLT, as well as their level of evidence. This systematic review followed the Preferred
58 Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and its
59 protocol was prospectively registered in PROSPERO (CRD42022320298).

60

61 **RESULTS**

62 Of the 2270 records identified, five CPGs were included: those from the European Geriatric
63 Medicine Society and the European Diabetes Working Party for Older People in 2022 (EuGMS-
64 EDWPOP22)⁵, the American Diabetes Association in 2022 (ADA22)⁶, the Endocrine Society
65 in 2019 (ES19)⁷, the Diabetes Canada Clinical Practice Guidelines Expert Committee in 2018
66 (DC18)⁸ and the network Deprescribing.org in 2017 (Deprescribing.org17)⁹ (Table 1). They
67 were all of “high methodological quality” according to AGREE-II scoring. However, the
68 domains related to stakeholders’ involvement, applicability of the recommendations, and rigor
69 of the CPG development were lacking in all CPGs. All CPGs provided a list of different profiles
70 of patients for whom deprescribing GLT is recommended, either because those patients have
71 an important risk of hypoglycemia (patients with advancing age, tight glycemic control,
72 prescription of hypoglycemic medications (sulfonylureas, glinides, or insulins), multiple
73 comorbidities, frequent hypoglycemia, impaired renal function, polypharmacy, or long duration
74 of diabetes), or because the benefit of GLT is uncertain (patients with severe neurocognitive
75 disorder, frailty, limited life expectancy or patients living in nursing home). These profiles are
76 heterogeneous between CPGs, and their definitions were unclear (Table 1). EuGMS-
77 EDWPOP22 and Deprescribing.org17 provided the most comprehensive lists of profiles,
78 whereas ES19 only suggest deprescribing for patients with severe neurocognitive disorder. The
79 extracted recommendations were of very low-level of evidence (mainly based on observational
80 studies, or opinions of experts).

81

82 **DISCUSSIONS**

83 This systematic review demonstrated the existence of specific recommendations defining the
84 profiles of patients in whom deprescribing is suggested, which is reassuring given the challenge
85 of avoiding overtreatment by GLT in older patients. However, there is room for improvement
86 in some aspects of the methodological development of these guidelines, such as improving the
87 diversity of experts involved in drafting the guidelines (e.g., experts in geriatrics and nursing),
88 empowering patients, and providing more clear and precise recommendations to increase their
89 easier use in daily clinical practice¹⁰. We have also highlighted a lack of consistency in the
90 content of recommendations between the CPGs, and a poor level-of-evidence of these
91 recommendations. There is indeed a significant lack of evidence in the area of T2D in older
92 people, especially in relation to overtreatment, and even more so to deprescribing GLT ¹. This
93 critically prevents the availability of quality recommendations in this crucial area.

94 Therefore, there is an urgent need for high-quality evidence in this field, necessary to establish
95 trustworthy recommendations, leading to the avoidance of overtreatment, and to better care of
96 older patients with type 2 diabetes.

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130 TABLES

131 **Table 1.** Profiles of patients to be targeted for de-prescribing glucose-lowering therapy (GLT)
 132 according to the recommendations of the five CPGs.

CPG	EuGMS-EDWPOP22 ⁵	ADA22 ⁶	ES19 ⁷	DC18 ⁸	Deprescribing.org 17 ⁹
	European Geriatric Medicine Society; European Diabetes Working Party for Older People	American Diabetes Association (ADA)	Endocrine Society	Diabetes Canada	Deprescribing.org network
Year	2022	2022	2019	2018	2017
Country / region	Europe	USA	USA (and Europe)	Canada	Canada
Nb of recomm. *	3/133	1/20	1/35	2/13	3/3
PATIENTS AT RISK OF HYPOGLYCAEMIA	Multiple comorbidities (esp. ≥ 5 comorbidities)	-	-	Multiple comorbidities	Multiple comorbidities
	Tight glycemic control ^a	-	-	-	Tight glycemic control
	Frequent hypoglycemia (esp. serious episodes needing assistance)	Wide glucose excursions or severe or recurrent hypoglycemia on sulfonylureas or glinides ^b	-	-	Hypoglycemia history or lack of awareness
	Inappropriate medications (esp. insulin or sulfonylureas)	Sulfonylureas or glinides (+ cognitive dysfunction, depression, anorexia, or inconsistent eating pattern)	-	-	Taking a sulfonylurea or insulin
	-	Polypharmacy ^b	-	-	Drug interactions
	Impaired renal function ^c	-	-	-	Impaired renal function
	Advancing age (≥ 80 years)	-	-	-	Advancing age
	Long duration of diabetes (> 20 years)	-	-	-	-
PATIENTS IN WHOM BENEFIT IS UNCERTAIN	Dementia, especially those with erratic eating pattern and abnormal behavior.	Cognitive dysfunction, depression, anorexia or inconsistent eating pattern (with sulfonylureas or glinide)	Cognitive impairment (i.e., mild cognitive impairment or dementia)	-	Dementia
	Significant weight loss, especially unintentional indicating frailty.	-	-	Frailty	Frailty
	End of life, especially those with ≤ 1 year life expectancy.	If taking any medications without clear benefits in approving symptoms and/or comfort (in patients at the end of life)	-	-	Limited life expectancy
	Nursing home residents, especially those with multiple comorbidities.	-	-	-	-

OTHER	-	-	-	-	Patients at risk of other GLT adverse effects
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133 * Number of recommendations extracted / Total number of recommendations provided in the
134 CPG; ^a HbA1c <6.5% or <7.0% in patients with frailty; ^b In patients in good or intermediate
135 health status; ^c especially those with end stage renal disease. CPGs: clinical practice guidelines;
136 esp.: especially

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