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RESEARCH ARTICLE

Treatment

Diabetes overtreatment and flags for deprescribing glucose-lowering treatment in geriatric inpatients with type 2 diabetes: Prognostic insights from a longitudinal cohort

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Abstract

Aims: The study investigated diabetes overtreatment (excessively intensive therapy) and flags for considering deprescribing glucose-lowering treatment (GLT) (clinical features identifying patients most likely to benefit from reducing treatment) in older adults with type 2 diabetes (T2D) and their association with five-year survival in geriatric inpatients.

Methods: Single-centre retrospective cohort study including geriatric inpatients hospitalised between 2008 and 2015, aged ≥75 years with T2D on GLT. Diabetes overtreatment, according to the 2019-Endocrine Society guidelines, was retrospectively defined based on the patient's health status, level of HbA1c and presence of inducing hypoglycaemia GLT. Flags for deprescribing were selected from a systematic review of recommendations for GLT deprescribing in older diabetic adults.

Results: Of the 447 inpatients (women: 52.8%; median age: 83 years), 89% had a poor health status, 55.2% were overtreated, and 99.5% had at least one deprescribing flag, and 44% of patients with ≥1 deprescribing flag were not overtreated. Over the five-year follow-up, median survival time after hospitalisation was 1.83 years [IQR, 1.56–2.09], with an 18% five-year survival [95%CI, 15%–22%]. Both overtreatment (HR [95%CI] 1.29 [1.04;1.58]) and accumulation of flags for deprescribing (HR [95%CI] 1.20 [1.11;1.29] per additional flag) were associated with increased mortality. Patients meeting both ≥4 flags for deprescribing and overtreated had the worst survival outcomes (10% five-year survival rate).

Conclusion: The cumulative burden of deprescribing flags provided complementary information beyond the current overtreatment definition. Patients classified as overtreated and combining several deprescribing criteria highlight a particularly vulnerable subgroup of patients with poor survival in which GLT use should be systematically reassessed.

KEYWORDS
depprescribing, glucose-lowering treatment, health status, older adults, overtreatment, type 2 diabetes

1 | INTRODUCTION

The management of glycaemic control through glucose-lowering treatment (GLT) in older adults with type 2 diabetes (T2D) presents unique challenges. This population is highly heterogeneous in terms of health status and life expectancy, leading to significant variability in the long-term benefits of treatment.[1,2] At the same time, GLT carries risks of adverse effects, particularly hypoglycaemia. While hypoglycaemia should be avoided in all individuals, certain patient profiles, especially those who are more vulnerable, are at higher risk for severe complications.[3]

To identify and mitigate inappropriate GLT, clinical practice guidelines over the past decade have addressed this issue from two complementary perspectives: overtreatment and deprescribing. One the one hand, overtreatment refers to a 'too intense treatment', or a therapeutic strategy that potentially causes more harms than benefits.[4] In older adults with T2D, diabetes overtreatment is commonly defined as maintaining HbA1c levels below predefined, health status-specific upper thresholds (<7%, <7.5% and <8% for patients with good, intermediate and poor health, respectively) while receiving glucose-lowering therapies associated with a high risk of hypoglycaemia (i.e. insulin, sulfonylureas or glinides).[5] On the other hand, deprescribing is 'the intentional and systematic reduction or discontinuation of medications that may no longer be beneficial or may cause harm'.[6] In the context of diabetes, recommendations identified different flags for considering deprescribing, that is features that can indicate that a person is a candidate in which to consider deprescribing.[7] These flags include age ≥80 years, malnutrition, estimated glomerular filtration rate (eGFR) <30 mL/min, cognitive impairment, Hba1c <7%, nursing home resident, a comorbidity count of ≥5 and polypharmacy of ≥10 prescribed drugs.

Although the concepts of glucose-lowering overtreatment and GLT deprescribing appear to be aligned, the degree of their overlap (or interchangeability) remains uncertain, leading to potential confusion among healthcare providers. This study aimed to investigate[1] the prevalence of diabetes overtreatment and flags for considering deprescribing (primary objective) and[2] the association between diabetes overtreatment, flags for deprescribing and five-year survival in geriatric inpatients with T2D. By examining these relationships, our findings seek to clarify the relevance of identifying overtreatment and/or flags for considering deprescribing in clinical practice, ultimately to contribute to optimised diabetes management in this vulnerable population.

What's new?

What is already known?

- Diabetes overtreatment in older adults is commonly defined using HbA1c thresholds and hypoglycaemia-prone therapies.
- Separate guideline-based 'flags' for considering deprescribing glucose-lowering treatment exist, but their value beyond overtreatment definition remains unclear.

What this study has found?

- In geriatric inpatients with type 2 diabetes, the cumulative burden of deprescribing flags strongly reflects patients' vulnerability.
- The cumulative number of deprescribing flags was strongly associated with poor survival.

What are the implications of the study?

- The cumulative burden of deprescribing flags may provide clinically relevant information beyond current overtreatment definitions and help guide treatment reassessment in geriatric inpatients adults.

2 | METHODS

2.1 | Study design

This retrospective cohort study was nested within two combined cohorts. The two original cohorts were created using similar data from the electronic medical records of inpatients from the same university hospital (Cliniques Saint-Luc, Brussels, Belgium). Patients in the first cohort were recruited from acute geriatric units[8] and in the second cohort from non-geriatric units (medical or surgical). The data of the patients' first hospital stay (in case of several hospitalisations) between 2008 and

2015 was collected. Patients were eligible if they were aged 75 years or older, had type 2 diabetes treated with GLT before their hospital stay, had undergone a HbA1c measurement in the last three months (see below) and a comprehensive geriatric assessment during their hospital stay.

Type 2 diabetes was defined according to the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus.[9] GLT included biguanides (metformin), sulfonylureas, glinides, insulins and other drugs (i.e. dipeptidyl-peptidase 4 inhibitor, glucagon-like peptide 1 receptor agonist, alpha-glucosidase inhibitors and thiazolidinediones). Sulfonylureas, glinides and insulins were considered GLT with high risk of hypoglycaemia.

Baseline characteristics and drug review were defined on the date of hospital admission. Patients' characteristics were collected as they were just before baseline. Follow-up started at baseline and ended after death or 5 years after inclusion, whichever came first.

2.2 | Survival outcomes

The patient's vital status was collected using the Belgian national Register, five years after the hospital admission, this time frame being suited for the study population.

2.3 | Covariates, diabetes overtreatment and flags for deprescribing

Patients' characteristics were collected from their electronic medical record, including sex, age, list of comorbidities, results of CGA (including functional status, cognition, nutrition), detailed GLT (prescribed before hospital stay), number of drugs by day (prescribed before hospital stay), HbA1c value (closest value to the date of discharge from hospital, measured within 3 months before this date) and estimated glomerular filtration rate (GFR) computed by the MDRD formula.

Diabetes overtreatment was determined based on the 2019 Endocrine Society guidelines as used in previous studies.[8,10,11] Overtreatment was thus considered present in older individuals treated with insulin, sulfonylureas or glinides (i.e. GLT with high risk of hypoglycaemia) if their HbA1c levels were below 7.0% (53 mmol/mol), 7.5% (58 mmol/mol) or 8.0% (64 mmol/mol), respectively, for patients in good, intermediate and poor health status. As in the 2019 Endocrine Society guidelines, patients' health status was defined according to the three-tiered classification of Blaum et al.[12]: good health (absence of diabetic comorbidities, ≤2 non-diabetes chronic illnesses, no impairment of basic Activities of Daily Living (ADL) and ≤1 instrumental ADL impairment), intermediate health (≥3 non-diabetes chronic illnesses, mild cognitive impairment/early dementia or ≥2 IADL impairments) and poor health (end-stage medical condition, moderate/severe dementia, ≥2/5 ADL impairments or residence in a long-term nursing facility).

The flags for considering GLT deprescription were selected based on a 2023 systematic review of the recommendations (low level of evidence) from recent major clinical practice guidelines on the GLT deprescription in older people.[7] They included advanced age (≥80 years), malnutrition (diagnosed by a dedicated hospital dietician based on patient's history of appetite loss, weight loss, eating habits as their evolution over time most often using the Minimal Nutrition Assessment – Short Form ≤7/14), impaired renal function (estimated GFR < 30 mL/min/1.73m^2), neuro-cognitive impairment (diagnosed dementia or MMSE <24/30), tight glycaemic control (HbA1c < 7.0% [< 53 mmol/mol]), nursing home residency, multiple comorbidities (≥5 different comorbidities) and polypharmacy (≥10 different drugs by day before hospital stay).

2.4 | Statistical analyses

Statistical analysis was performed using R (version 4.3.2), R Core Team, Vienna, Austria, 2022.[13] Continuous data were described as medians and interquartile ranges [IQR], and categorical data were expressed as number of people and percentages. Data among patient groups were compared using Wilcoxon rank test for numeric data and Pearson's chi-squared test for categorical data. The distribution of overtreatment and flags for deprescribing was expressed as the number and percentage of patients sharing the same set of conditions (i.e. overtreatment and/or flags for deprescribing). Combinations of at least two conditions were referred to as intersections (e.g. multimorbidity and cognitive impairment). The intersections were represented graphically, using an Upset plot (UpsetR package[14]). Survival was assessed during the 5-year follow-up using Kaplan–Meier curves and a two-sample Log-Rank test to compare strata (overtreatment and ≥4 deprescribing flags). Univariable Cox Proportional Hazard regression analysis was used to assess the association between conditions calling for GLT deprescription and diabetes overtreatment (presented as Hazard Ratio (HR) [95% Confidence Intervals (95%CI)]) and 5-year survival. Restricted cubic spline modelling was used to evaluate the linearity of the additive effect of deprescribing criteria. A multivariable Cox regression model was computed to assess which flags were most associated with mortality risk. This model

was built, incorporating flags for deprescribing with a p-value <0.1 and additional potential confounders with a p-value <0.1 in univariable analysis (sex and hospitalisation context). Absence of collinearity was tested using the Variance Inflation factor (VIF). Survival data was censored at five years. The proportional hazards assumption was assessed for all Cox regression models using tests based on scaled Schoenfeld residuals and by visual inspection of the corresponding residual plots. Throughout the analysis, a p-value below 0.05 was considered statistically significant.

3 | RESULTS

3.1 | Patients' characteristics

A total of 447 patients (median age 83 years [IQR, 80–87 years], 236 (52.8%) women were included in the study), with 318 (71.1%) admitted to acute geriatric units and 129 (28.9%) from non-geriatric units assessed by the geriatric liaison team (Table 1) (Table S1). Poor health status was present in 400 patients (89%), with the remaining 47 ones (11%) in intermediate health status. No patient was in good health status. Functional impairment (2 or more dependencies in activities of daily living) was present in 258 (58%) patients, and 87 (19%) patients lived in nursing homes. They were prescribed a median number of 9 [IQR, 7–11] different drugs per day. The median amount of GLT use was of 1 [IQR, 1–3] drug, with 328 (73.4%), 105 (23.5%) and 14 (3.1%) taking 1, 2 and ≥3 different GLT drugs, respectively. GLT with high risk of hypoglycaemia (sulfonylureas, glinides or insulin) was prescribed in 351 (78.5%) of patients (sulfonylureas/glinides in 57.5% and insulin in 31%). Metformin was prescribed in 193 patients (43.2%), other non-hypoglycaemic GLT being very infrequent. The median HbA1c was 6.9% [IQR, 6.2–7.8%] (52 mmol/mol [IQR, 44–62 mmol/mol]) (Table 1).

TABLE 1 Patients' general characteristics.

Variables	Patients $N = 447$[1]
Age, *in years*	83 [80, 87]
Women	236 (52.8)
Nursing home	87 (19.5)
ADL dependency (2 or more)	258 (57.7)
Health status	
Intermediate	47 (10.5)
Poor	400 (89.5)
Number of drugs by day	9 [7, 11]
Cognitive impairment	224 (50.1)
Daily number of GLT	1 [1, 3]
1 GLT	328 (73.4)
2 GLT	105 (23.5)
3 or more GLT	14 (3.1)
Metformin use	193 (43.2)
Hypoglycaemic agents use (any)	351 (78.5)
Insulin use	139 (31.1)
Sulfonylureas, glinides	229 (51.2)
HbA1c, *in % (mmol/mol)*	6.90 [6.20, 7.80] (52 [44, 62])
Hospital division	
Geriatric	318 (71.1)
Non-geriatric	129 (28.9)

Abbreviations: ADL, Activities of daily living. GLT, Glucose-lowering treatment.

[1]Median [interquartile range] or *n* (%).

3.2 | Overtreatment and conditions calling for GLT deprescribing

According to the definition of overtreatment derived from the Endocrine Society's recommendations, 248 patients (55.4%) were overtreated, based on the GLT type (presence of hypoglycaemic drug or not) and the HbA1c level. According to international guidelines, 445 patients (99.5%) had at least one of the eight conditions calling for the GLT deprescription (Table 2). Notably, three-quarters (74%) of the patients presented three or more of these conditions. Among the 447 patients, 79% were aged 80 years or more, 58% had ≥5 comorbidities, 50% had cognitive impairment, and 47.2% had HbA1c < 7% (Table 2).

Regarding the overlap between overtreatment and the presence of conditions calling for GLT deprescription, 197 of the 445 patients (44.3%) with ≥1 condition calling for deprescription were identified as not overtreated (Figure 1a). The proportion of patients identified as not overtreated is similar (44% – 41%) up to 3 conditions calling for GLT deprescription. In those with 4, 5 and 6 flags for deprescribing, 36.8%, 35.2% and 23.1% were not identified as overtreated, respectively.

In examining how conditions suggesting GLT deprescribing cluster among patients, we identified that the 3 most frequent combinations of flags for deprescribing (present in 31, 31 and 29 patients, Figure 1b) combine at least 3 of the 5 most frequent flags for deprescribing (age ≥80 years, ≥5 comorbidities, cognitive impairment, HbA1c < 7%, use of ≥10 drugs daily). More importantly, 2 out of these 3 most frequent combinations combine 4 and 5 of those most frequent flags for deprescribing. Interestingly, an important proportion of those patients

TABLE 2 Overtreatment and flags for deprescribing.

Variables	All patients $N=447$[1]
Overtreatment	
Overtreated	248 (55.5)
No overtreatment	199 (44.5)
Number of flags for deprescribing	3 [2; 4]
$n \geq 1$	445 (99.6)
$n \geq 2$	416 (93.1)
$n \geq 3$	333 (74.5)
$n \geq 4$	212 (47.4)
Prevalence of flags	
Advanced age (≥80 years)	352 (78.7)
Tight glycaemic control (< 7%, < 53 mmol/mol)	212 (47.4)
Impaired renal function (< 30 mL/min)	79 (17.7)
Nursing home	87 (19.4)
Multimorbidity (≥5 different comorbidities)	258 (57.7)
Polypharmacy (≥10 different drugs/day)	199 (44.5)
Cognitive Impairment	224 (50.1)
Malnutrition	125 (28.0)

Abbreviations: GLT, glucose-lowering treatment.

[1] *n* (%) or Median [Interquartile range].

(combining the most frequent flags for deprescribing) remain identified as not overtreated (Figure 1b).

3.3 | Survival

Except for 3 patients, all patients ($n=444$) had a complete 5-year follow-up. The median survival time was 1.83 years [IQR, 1.56–2.09], and at 5 years, 82 patients were alive, resulting in a survival probability of 18% [95%CI, 15%–22%] (Figure S1). The higher risk of mortality was observed during the first year of follow-up.

From univariable Cox regression analysis, overtreatment was associated with 29% increased risk of 5-year mortality (HR, 1.29 [95%CI, 1.04–1.58], $p=0.018$: Table S2) and ≥4 deprescribing flags with a 56% increased risk (HR, 1.56 [95%CI, 1.27–1.92], $p<0.001$, Table S2). Each additional flag for deprescribing further increased the risk of mortality by 20% (HR, 1.20 [95%CI, 1.11–1.29], $p<0.001$; Figure 3, Table S2). Interestingly, patients combining both overtreatment and ≥4 flags for deprescribing had the worst probability of 5-year survival, as low as 10% (Figure 2). Median survival time of patients with both overtreated and ≥4 flags for deprescribing was 1.06 years [95%CI, 0.67–1.79], whereas it was 2.54 years [95%CI, 2.01–3.87] in those with no overtreatment and <4 flags for deprescribing.

In a head-to-head multivariable survival analysis with both overtreatment and the number of deprescribing flags, only deprescribing flags remained significant (HR 1.17 [95%CI, 1.08–1.26] per additional flag, $p<0.001$) (Table S3). These findings suggest that the excess risk associated with overtreatment may be largely explained by the underlying burden of deprescribing flags. Furthermore, the association between the number of deprescribing criteria and mortality did not differ according to overtreatment status (P for interaction = 0.56).

Among the flags for deprescribing, malnutrition, impaired renal function, nursing home residency and multimorbidity were the main risk factors for 5-year mortality (Figure 3).

4 | DISCUSSION

This cohort study in geriatric inpatients with type 2 diabetes and a median age of 83 years found a high prevalence of diabetes overtreatment (55%) and of any deprescribing flag (99%). The near-universal presence of at least one deprescribing flag highlights the high burden of vulnerability in this population. The survival rate of geriatric patients with diabetes after a hospitalisation is remarkably low, with a median survival of less than 2 years and only 18% remaining alive at 5 years. Both diabetes overtreatment and the accumulation of flags calling for GLT deprescribing were associated with worse survival over the 5-year follow-up, with the poorest outcomes observed in patients meeting both conditions. Notably, each additional deprescribing flag was linked to a 20% increase in mortality risk over five years.

Overtreatment and flags for considering GLT deprescription reflect two distinct perspectives on inappropriate diabetes treatment that is, treatment that potentially causes more harm than benefit. However, this study shows that these two approaches provide complementary information to support treatment optimisation in these patients. Using the overtreatment criteria of the 2019 Endocrine Society guidelines, half of this hospitalised geriatric cohort was not considered overtreated, despite a median HbA1c of 6.9% and strong clinical grounds to question the appropriateness of GLT in nearly all patients. This level of glycaemic control is strikingly low in a cohort in which 89% of patients were classified as being in poor health and probably deserves greater clinical attention. This discrepancy was already suggested in another cohort study conducted in US nursing homes residents with T2D, where only 27% of the residents with overtreatment (insulin therapy and HbA1c < 7%) had GLT deintensified 14 days after HbA1c measurement.[15] Taken together with the poor prognosis of older patients with diabetes

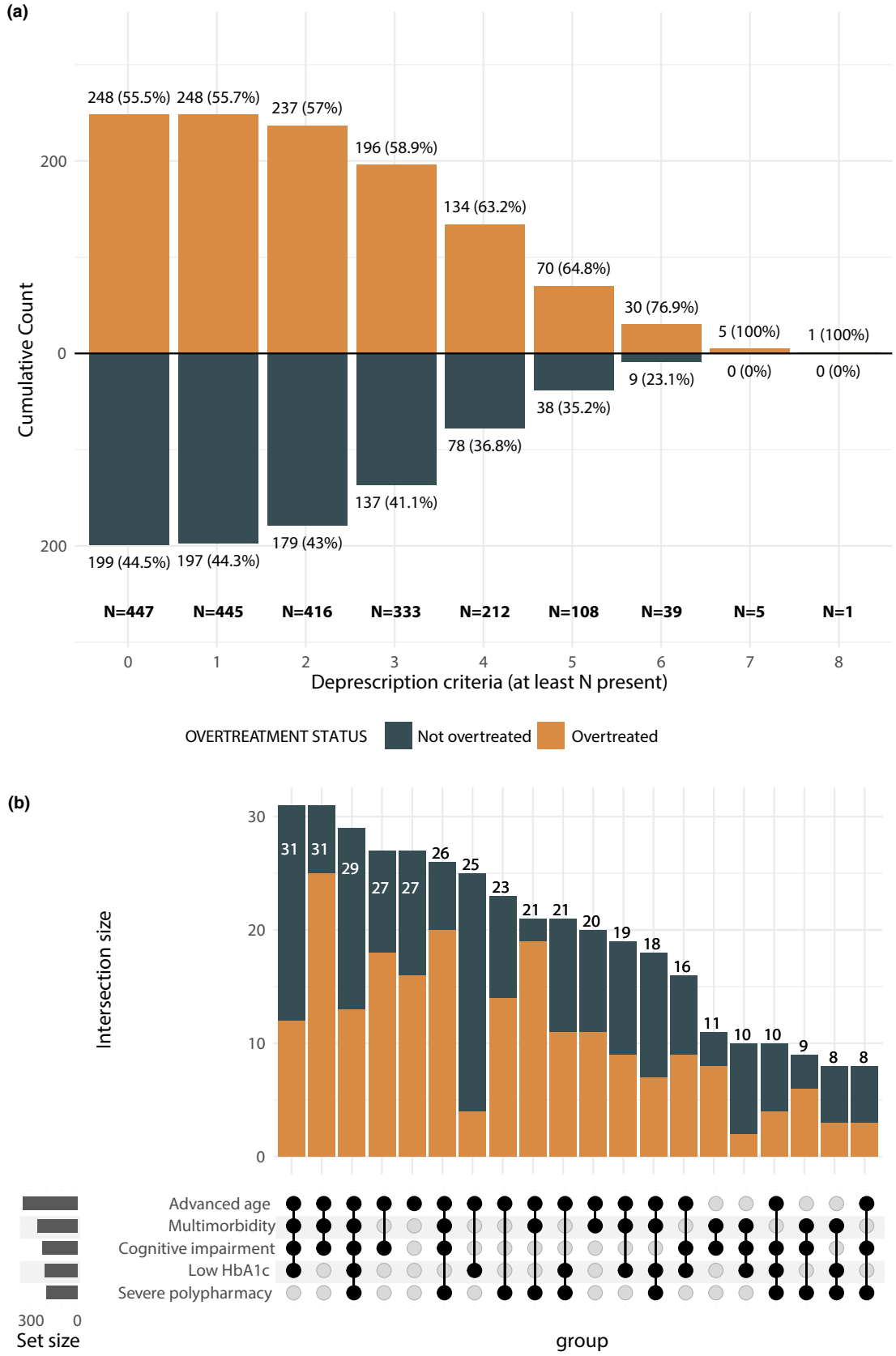

FIGURE 1 Distribution of overtreatment and flags for deprescribing. (a) Overtreatment status according to the cumulative count flags for deprescribing. Percentages are given per cumulative count group (N overtreatment group/N patients with at least N flags present). (b) UpSet plot representing co-occurrence of overtreatment and the five most prevalent flags for deprescribing. Numbers on the bars indicate the total count of patients within each intersection.

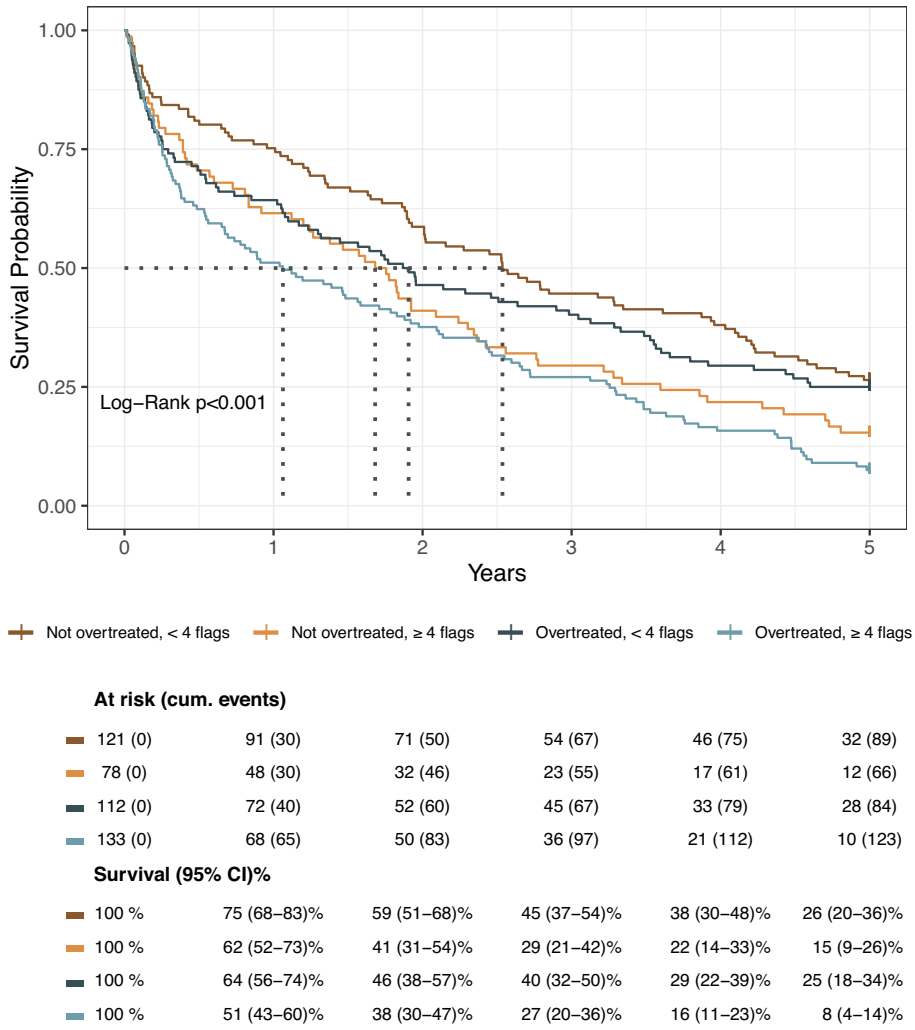

FIGURE 2 Kaplan–Meier survival curve stratified by overtreatment and deprescription flags. Five-year survival of geriatric inpatients with type 2 diabetes, stratified according to overtreatment and ≥4 flags for deprescribing. Pointed lines indicate median survival for each strata.

after hospitalisation, this finding underscores the value of re-evaluate treatment goals in hospitalised patients with geriatric conditions.[16]

More importantly, our results expose key limitations of the current definitions of diabetes overtreatment.[5,10,17] Our recent review identified 12 definitions, 8 of which not considering the patient's health status to individualise the glycaemic treatment goal.[5] Previous studies have also shown that overtreatment fails to effectively identify patients at risk of hypoglycaemia.[18,19] More importantly, current overtreatment definitions do not address an increasingly common clinical question: whether glucose-lowering drugs, other than sulfonylureas, glinides and insulin, should be deprescribed in frail older adults. In contrast, the eight flags for deprescribing take a more holistic approach, emphasising the patient's clinical context, vulnerability to treatment-related harm and the limited benefits they may reasonably expect. These flags include major geriatric syndromes (such as neuro-cognitive impairment, malnutrition, multiple, major polypharmacy) and other predictors or surrogates of frailty (nursing home residency, multiple comorbidities, severe renal impairment). Of note, the STOPP version 3 does not mention flags for deprescribing, except the criterion J1 (sulphonylureas with long half-time, that is glibenclamide, chlopropamide, glimepiride). More recently, this broader perspective has been conceptualised as treatment realignment, a patient-centred approach aiming to continuously adapt diabetes management to changes in health status, vulnerability and goals of care rather than relying primarily on HbA1c threshold.[20] The eight deprescribing flags identified in our study closely align with the 'triggers' proposed in the 4S Pathway (i.e. 'Seeking triggers, Shared decision making, Setting goals, Simpler and safer regimens').

The five-year survival analysis supports the clinical utility of the 8 flags for GLT deprescribing: they identify

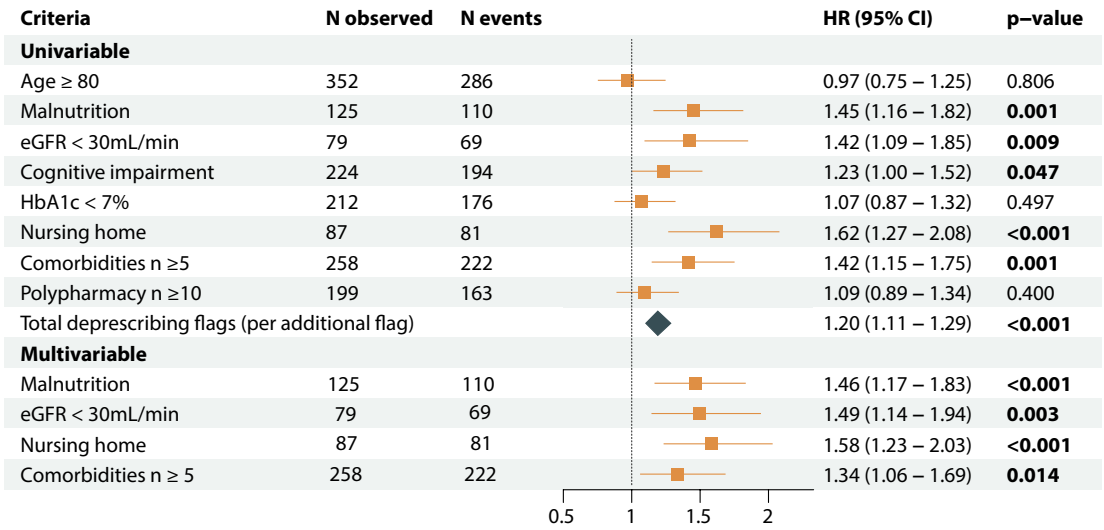

FIGURE 3 Forest plot of mortality risk associated with conditions calling for GLT prescription. Univariable and multivariable Cox regression of flags for deprescribing. N observed are the number of patients with the given flag for deprescribing. N events are the number of patients with the flag who died within 5 years. Multivariable analysis was additionally adjusted for sex and context of hospitalisation. GLT, Glucose-lowering treatment; HR, Hazard ratio; 95% CI, 95% Confidence interval; eGFR, estimated glomerular filtration rate.

patients with a very limited life expectancy for whom the long-term benefits of intensive treatment (i.e. overtreatment) are probably very limited. This was further supported by the head-to-head multivariable analysis, in which the association between overtreatment and mortality was attenuated after accounting for the cumulative burden of deprescribing flags. These findings should be interpreted as identifying patients in whom glycaemic treatment goals may warrant re-evaluation, rather than suggesting that deprescribing itself would improve survival. Our findings suggest this is especially true for patients living in nursing homes, those with multiple comorbidities, malnutrition or severely impaired renal function.

Our study has several limitations. First, our cohort consisted of older inpatients, most of whom had poor health status. While this enhances the relevance of our findings for a high-risk population, it limits their generalisability to healthier, community-dwelling older adults with diabetes and to healthcare settings with different prescribing practices or more contemporary diabetes management approaches. Second, due to the retrospective design, some key data were missing or unavailable, including markers of frailty, hypoglycaemic events and other measures allowing a more complete characterisation of patients' comorbidity burden. Additionally, this study lacks information on patients' and providers' preferences regarding GLT, which prevents a comprehensive understanding of the perceived risks and benefits that may have influenced GLT prescribing. HbA1c was measured within three months of hospitalisation. However, factors such as acute illness, malnutrition, renal dysfunction and anaemia could affect HbA1c levels, potentially impacting the classification of overtreatment. Finally, the low use of GLP-1 receptor agonists and SGLT2 inhibitors, together with the high use of sulfonylureas, should be interpreted in the context of the study period (2008–2015). Contemporary prescribing practices have substantially evolved following the widespread adoption of SGLT2 inhibitors and GLP-1 receptor agonists because of their cardiovascular and renal benefits.[21] Therefore, the observed treatment patterns and prevalence estimates of overtreatment may not fully reflect current clinical practice. Nevertheless, this limitation is less relevant for the interpretation of the deprescribing flags, which reflect patients' vulnerability rather than specific drug classes. Moreover, contemporary frameworks such as treatment realignment and the 4S Pathway emphasise treatment simplification and safer regimens, beyond specific glucose-lowering drug classes.[20] Note that the estimated glomerular filtration rate was calculated using the MDRD formula, whereas since 2021 the CKD-EPI equation has been used as the standard.

In conclusion, our findings suggest that the current individualised definition of diabetes overtreatment is insufficient to guide appropriate GLT adjustments in geriatric patients. To improve care for very old adults with type 2 diabetes, and to support clinicians navigating complex treatment decisions, there is a pressing need to move beyond existing definitions of diabetes overtreatment—or more broadly, inappropriate treatment—in this population, towards approaches that better support decisions about the appropriateness of continuing any glucose-lowering treatment according to patients' vulnerability, life expectancy and goal of care. Meanwhile, the use of the flags for deprescribing might guide clinicians to identify geriatric

patients with diabetes who may benefit from glycaemic treatment deintensification.

AUTHOR CONTRIBUTIONS

Antoine Christiaens had the original idea of the study and provided overall supervision. Christophe de Terwangne and Antoine Christiaens conceived the study design, conducted the statistical analyses and drafted the initial manuscript. All authors (Christophe de Terwangne, Séverine Henrard, Sophie Marien, Michael A. Steinman, Benoit B. Boland and Antoine Christiaens) critically reviewed the manuscript for important intellectual content and contributed to its revision.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest.

ETHICS STATEMENT

This study was approved by the Institutional Review Board (Commission d'Ethique Hospitalo-Facultaire, Cliniques universitaires Saint-Luc, Brussels, Belgium; IRB 00001530 – IRB 00008535; Approval ref. B 403/2018/20MAR/120 and B 403/2018/15JAN/015). According to the national regulations and approval of the Institutional Review Board (Commission d'Ethique Hospitalo-Facultaire, Cliniques universitaires Saint-Luc, Brussels, Belgium), there was no need for informed consent to participate in this retrospective study, as long as the investigators have verified the refusal of use of the retrospective data for scientific research issued by the patients.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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