

Diabetes Overtreatment and Hypoglycemia in Older Patients with type 2 Diabetes on Insulin Therapy:
Insights from the HYPOAGE Cohort study

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ONLINE-ONLY SUPPLEMENTAL MATERIAL

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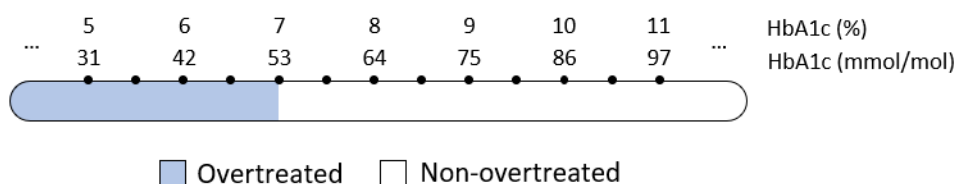
Supplemental Table S.1. Complementary methods information of HYPOAGE cohort and covariate definitions

Inclusion criteria	Patients from HYPOAGE cohort meeting the following criteria: outpatients aged 75 years or older, with T2D (duration of ≥ 1 year), treated by a glucose-lowering treatment including insulin for at least 6 consecutive months, with a HbA1c measure at baseline and who measured blood glucose using ≥ 2 self-monitoring blood glucose (SMBG) per day.
Exclusion criteria	Patients with type 1 diabetes, with corticosteroid-induced diabetes, with an estimated life expectancy lower than 6 months, or unable to follow the study procedures.
Ethics	The original study fulfilled all ethical requirements (approved by the independent ethical committee CPP Ouest IV, ref 47/16) and patients were enrolled after signing an informed written consent.
Covariates definitions	<p>Sociodemographic (age, sex), clinical (health status, comorbidities, diabetes duration, BMI, current medications including glucose-lowering treatment), biological (HbA1c and estimated glomerular filtration rate (eGFR) using the CKD-EPI formula) and geriatric data (comprehensive geriatric assessment) were collected at baseline. HbA1c was expressed as % (using the standards of the National Glycohemoglobin Standardization Program) and mmol/mol (using the standards of the International Federation of Clinical Chemistry).</p> <p>The comprehensive geriatric assessment was performed by a trained geriatrician and included physical performances (Timed Up and Go test, gait speed, and 5 times sit to stand test), functional status (Katz score (range: 0-6) for dependence in activities of daily living), cognition (Mini-Mental State Examination (MMSE) and Frontal Assessment Battery (BREF score); cognitive impairment: MMSE < 24/30 and/or BREF score < 16/18), major depressive disorder (Mini-Geriatric Depression Scale), and nutritional status (based on Body Mass Index and Mini-Nutritional Assessment). Frailty was defined according to the Fried definition. Health status was defined according to the three-tiered Blaum's classification (good, intermediate and poor health status), based on comorbidities, functional status, and cognitive status [Supplemental Figure S.1.].</p>
Predictive values calculation	<p>Sensitivity $\left[\frac{TP}{TP+FN} \right]$, specificity $\left[\frac{TN}{TN+FP} \right]$, and accuracy $\left[\frac{TP+TN}{TP+TN+FP+FN} \right]$, considering true positive (TP) as the proportion of hypoglycemic patients with overtreatment, true negative (TN) as the proportion of non-hypoglycemic patients without overtreatment, false negative (FN) as the proportion of hypoglycemic patients without overtreatment, and false positive (FP) as the proportion of non-hypoglycemic patients with overtreatment. All measures of diagnostic performances were presented with their 95% confidence interval.</p> <p>Mc Nemars's tests compared diagnostic performances between the two different proxy-definitions of overtreatment.</p>

Supplemental Figure S.1. Proxy-Definitions of diabetes overtreatment (patients on insulin).

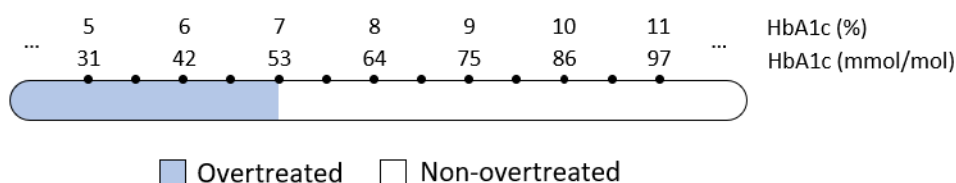
Abbreviations: ADL, activities of daily living; IADL, instrumental activities of daily living.

FIXED PROXY-DEFINITION OF DIABETES OVERTREATMENT

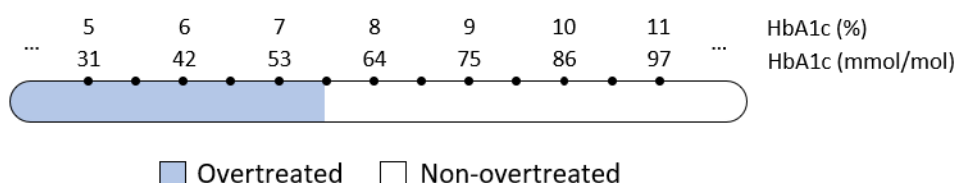


INDIVIDUALIZED PROXY-DEFINITION OF DIABETES OVERTREATMENT

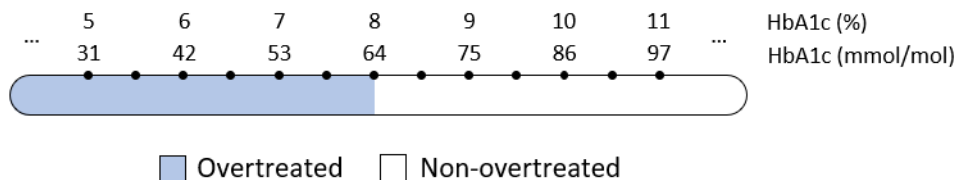
A. PATIENTS IN GOOD HEALTH STATUS *[absence of diabetic comorbidities, ≤ 2 non-diabetes chronic illnesses, no basic ADL impairments and ≤ 1 instrumental ADL impairment]*



B. PATIENTS IN INTERMEDIATE HEALTH STATUS *[≥ 3 non-diabetes chronic illnesses, mild cognitive impairment/early dementia or ≥ 2 IADL impairments]*

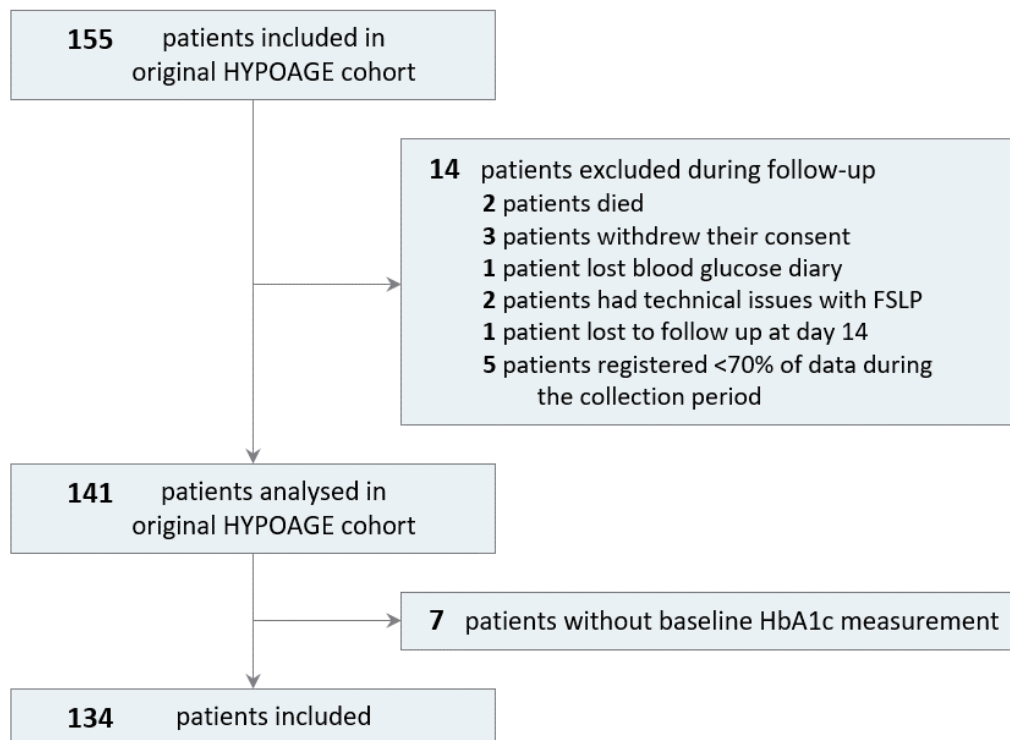


C. PATIENTS IN POOR HEALTH STATUS *[end-stage medical condition, moderate/severe dementia, $\geq 2/5$ ADL impairments or residence in a long-term nursing facility]*



Supplemental Figure S.2. Study flowchart.

Abbreviations: FSLP, FreeStyle Libre Pro® Sensor.



Supplemental Table S.2. Complementary baseline patient's characteristics according to the fixed and the individualized proxy-definitions of diabetes overtreatment, including data on diabetes treatment and diabetes co-morbidities

	Diabetes overtreatment fixed proxy-definition Mean \pm SD <i>or</i> n (%)			Diabetes overtreatment individualized proxy-definition Mean \pm SD <i>or</i> n (%)		
	No n=109 (81.3%)	Yes n=25 (18.7%)	p-value	No n=81 (60.4%)	Yes n=53 (39.6%)	p-value
Age \geq 85 years	35 (32.1%)	7 (28.0%)	0.690	25 (30.9%)	17 (32.1%)	0.883
Diabetes duration \geq 20 years	61 (65.6%)	14 (60.9%)	0.672	47 (67.1%)	28 (60.9%)	0.489
Insulin regimen						
Basal insulin	52 (47.7%)	11 (44.0%)	0.690	38 (46.9%)	25 (47.2%)	0.962
2 or 3 injections/day	22 (20.2%)	7 (28.0%)		17 (21.0%)	12 (22.6%)	
Basal-bolus or CSII	35 (32.1%)	7 (28.0%)		26 (32.1%)	16 (30.2%)	
GLD regimen ¹						
Monotherapy (insulin)	42 (38.5%)	14 (56.0%)	0.177	28 (34.6%)	28 (52.8%)	0.104
Bitherapy	31 (28.4%)	7 (28.0%)		25 (30.9%)	13 (24.5%)	
Tritherapy or more	36 (33.0%)	4 (16.0%)		28 (34.6%)	12 (22.6%)	

¹ Number of different GLD classes/day

Abbreviations: SD, Standard deviation; GLD, Glucose-lowering drug

Supplemental Table S.3. Comparison of CGM metrics according to overtreatment proxy-definitions
(fixed and individualized)

	Diabetes overtreatment, fixed proxy-definition Median [interquartile range]			Diabetes overtreatment, individualized proxy-definition Median [interquartile range]		
	No n=109 (81.3%)	Yes n=25 (18.7%)	p-value	No n=81 (60.4%)	Yes n=53 (39.6%)	p-value
Time of worn CGM, <i>days</i>	28.0 [22.0;29.0]	29.0 [27.0;29.0]	0.005	28.0 [24.0;29.0]	29.0 [27.0;29.0]	0.077
Time of active CGM, %	99.8 [99.6;100.0]	99.7 [99.7;100.0]	0.755	99.8 [99.6;100.0]	99.8 [99.6;100.0]	0.718
Mean glucose, <i>mg/dL</i>	154.2 [134.0;180.0]	123.3 [112.2;140.0]	< .001	157.1 [134.6;189.7]	137.2 [118.2;152.6]	< .001
Glucose management indicator (GMI), %	7.0 [6.5;7.6]	6.3 [6.0;6.7]	< .001	7.1 [6.5;7.8]	6.6 [6.1;7.0]	< .001
Glycemic variability (% CV), %	34.9 [29.8;40.2]	31.7 [29.0;35.7]	0.058	34.7 [30.0;40.2]	32.6 [29.2;37.7]	0.333
TAR , % (glycemia >180 mg/dL)	28.0 [15.4;44.7]	5.9 [2.7;16.6]	< .001	29.9 [18.3;51.2]	15.4 [4.0;26.7]	< .001
Level 2 TAR, % (glycemia >250 mg/dL)	5.2 [1.1;15.7]	0.0 [0.0;1.4]	< .001	5.8 [1.5;17.6]	0.6 [0.0;5.1]	< .001
Level 1 TAR, % (glycemia 181-250 mg/dL)	22.7 [12.9;28.1]	5.9 [2.7;16.2]	< .001	23.8 [15.7;30.4]	13.2 [3.8;20.7]	< .001
TIR , % (glycemia 70-180 mg/dL)	65.7 [50.0;78.3]	82.4 [73.1;90.0]	< .001	62.6 [46.7;75.6]	79.6 [64.2;86.1]	< .001
TIR (70-180 mg/dL), <i>hours/day</i>	15:45 [12:00;18:47]	19:46 [17:32;21:36]	< .001	14:43 [11:00;18:05]	19:09 [15:29;20:42]	< .001
TBR , % (glycemia <70 mg/dL)	2.6 [0.9;6.4]	6.3 [1.1;12.1]	0.059	2.6 [0.9;5.1]	4.1 [1.1;12.1]	0.077
Level 1 TBR, % (glycemia 54-69 mg/dL)	2.0 [0.6;4.1]	4.3 [1.1;6.1]	0.034	2.0 [0.6;3.6]	3.6 [0.9;6.1]	0.038
Level 2 TBR, % (glycemia <54 mg/dL)	0.7 [0.0;2.7]	0.9 [0.2;4.7]	0.140	0.7 [0.0;2.0]	0.7 [0.2;4.2]	0.239

Abbreviations: CGM, Continuous glucose monitoring; CV, coefficient of variation; TAR, Time above range; TBR, Time below range; TIR, Time in range.