

Title: Considering Deintensification and Deprescription of Higher HbA1c Targets in Vulnerable Older Adults with Type 2 Diabetes: A Retrospective Database Study

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Table S1. Diagnostic codes and EphMRA-ATC codes for identifying study population

Codes	
Type 2 diabetes	ICD-10 codes: E11–E14
Type 1 diabetes	ICD-10 code: E10
Glucose-lowering drugs	EphMRA-ATC codes: A10C: Insulin or insulin analogue A10H: Sulfonylurea A10J: Biguanide A10K: Thiazolidine A10L: α -Glucosidase Inhibitor A10M: Glinide A10N: DPP-4 inhibitor A10P: SGLT2 inhibitor A10S: GLP-1R agonist

ICD-10, International Classification of Diseases 10th Revision-10.

Table S2. Diagnosis, procedure and drug codes for identifying health status categories of blood glucose control targets

Health status		Codes
Moderate-to-severe dementia: ICD-10 codes AND drug codes listed below		
Dementia		ICD-10 codes: F00–F05, F060, G30, G310, G311, G318, G94, R418
Donepezil hydrochloride		Japanese drug ingredient code: 1190012
Galantamine hydrobromide		Japanese drug ingredient code: 1190019
Memantine hydrochloride		Japanese drug ingredient code: 1190018
Rivastigmine		Japanese drug ingredient code: 1190700
Comorbidities		
Chronic obstructive pulmonary disease		ICD-10 codes: J40–J44, J47
End-stage renal disease requiring dialysis		Japanese procedure codes: 113002510, 114003610, 114003510, 114009310, 114009410, 114006510, 114008250, 114006610, 114009510, 140008510, 140054950, 140054850, 140008770, 140008670, 140008810, 140057810, 140057910, 140058010, 140060210, 140060310, 140060410, 140058110, 140058210, 140058310, 140060510, 140060610, 140060710, 140058410, 140058510, 140058610, 140060810, 140060910, 140061010, 140007710, 140007910, 140058770, 140058870, 140033770, 140058970, 140055970, 140059070, 140059170, 140029850, 140059270, 140053670, 140051110, 140051010, 140036710, 140052810, 140008170, 140052570, 140052970
Chronic kidney disease excluding dialysis		ICD-10 codes: E112, E132, E142, I12, I13, I150, I151, N00–N08, N11, N12, N14–N16, N18, N19, N25–N28, N391, N392, E851, D593, B52, Q60–Q63
Fracture		ICD-10 codes: S02, S12, S22, S32, S72, S82, S92, T02, T08, T12, M80, T142
Myocardial infarction		ICD-10 codes: I21, I22, I252
Congestive heart failure		ICD-10 codes: I099, I110, I130, I132, I255, I420, I425–I429, I43, I50, P290
Cerebrovascular disease		ICD-10 codes: G45, G46, H340, I60–I69

Malignancy (excluding malignant skin neoplasm)	ICD-10 codes: C00–26, C30–C41, C43, C45–C58, C60–C76, C81–C88, C90–C97
Cirrhosis	ICD-10 codes: K703, K743–K746
Peripheral arterial disease	ICD-10 codes: I702 Japanese standardized diagnostic codes: 4409028, 8839948

ICD-10, International Classification of Diseases 10th Revision-10.

Table S3. Diagnostic codes and drug codes for identifying severe hypoglycemia

	Codes
Hypoglycemia-related diagnosis	ICD-10 codes: E110, E120, E130, E140, E15, E160, E161, E162.
Glucose infusion	
20% glucose infusion	Japanese receipt processing system drug codes: 620006647, 620155611, 620155640, 620155641, 621651401, 640408013, 640421002, 640431047, 643230042, 643230298, 620155645, 620155634
40% glucose infusion	Japanese receipt processing system drug codes: 620006648, 643230047, 643230314
50% glucose infusion	Japanese receipt processing system drug codes: 620002599, 620006649, 640460006, 643230048, 643230317, 620155716, 620155714
Glucagon infusion	Japanese receipt processing system drug codes: 620007279, 621197401, 621515302

ICD-10, International Classification of Diseases 10th Revision-10.

Table S4. Diagnostic codes for other comorbid conditions

Comorbid conditions	Codes
Diabetic retinopathy	ICD-10 codes: E113, E143, H360
Diabetic neuropathy	ICD-10 codes: E114, E144
Hypertension	ICD-10 codes: I10, I11, I12, I13, I15, I16
Arthritis	ICD-10 codes: M05, M06, M120, M352, M45, M461, M468, M469, M498, M353
Urologic diseases or conditions	ICD-10 codes: N301, N320, N393, N394, N40, R32 Japanese standardized diagnostic codes: 8843031, 8844583
Depression	ICD-10 codes: F32, F33

ICD-10, International Classification of Diseases 10th Revision-10.

Table S5. Covariates included in the negative binomial regression models for severe hypoglycemia (overall cohort and models stratified by JDS/JGS category: Category I+II and Category III)

Feature	Variable	Overall	Category I + II	Category III
Group	Category I + II	Yes	No	No
	Category III	Yes	No	No
Patient demographics	Age	Yes	Yes	Yes
Comorbidities	Dementia	No	Yes	No
	Kidney disease	No	Yes	Yes
	Diabetic neuropathy	Yes	Yes	Yes
	Hypertension	Yes	Yes	No
	Arthritis	Yes	Yes	No
	Urologic diseases or conditions	Yes	No	No
	Depression	Yes	No	No
	Prior severe hypoglycemia	Yes	Yes	Yes
	Congestive heart failure	No	Yes	Yes
	Cerebrovascular disease	No	Yes	No
	Malignancy, except malignant neoplasm of skin	No	Yes	Yes
	Fracture	No	Yes	No
	Diabetic retinopathy	No	Yes	Yes
	Chronic obstructive pulmonary disease	No	No	Yes
	Cirrhosis	No	No	Yes
	Peripheral Arterial Disease	No	No	Yes
Glucose-lowering medication used	Biguanide	Yes	Yes	Yes
	DPP-4i	Yes	Yes	Yes

SGLT2i	Yes	Yes	Yes
Glinide	Yes	Yes	Yes
Sulfonylurea	Yes	Yes	Yes
GLP-1RA, Thiazolidine, Alpha-glucosidase inhibitor	Yes	Yes	Yes
Insulin (Basal insulin, other insulins)	Yes	Yes	Yes
Sulfonylurea plus [Biguanide, DPP-4i, SGLT-2i, Glinide, Thiazolidine, Alpha-glucosidase inhibitor, GLP-1RA]	Yes	Yes	Yes
Glinide plus [Biguanide, DPP-4i, SGLT-2i, Thiazolidine, Alpha-glucosidase inhibitor, GLP-1RA]	Yes	Yes	Yes
Basal insulin plus [Biguanide, DPP-4i, SGLT-2i, Glinide, Sulfonylurea, Thiazolidine, Alpha-glucosidase inhibitor]	Yes	Yes	Yes
Basal insulin plus GLP-1RA	Yes	Yes	Yes
Other insulins plus [Biguanide, DPP-4i, SGLT-2i, Glinide, Sulfonylurea, GLP-1RA, Thiazolidine, Alpha-glucosidase inhibitor, Basal insulin]	Yes	Yes	Yes
DPP-4i plus [Biguanide, SGLT-2i, Thiazolidine, Alpha-glucosidase inhibitor, GLP-1RA]	Yes	Yes	Yes
Other combination therapy (2 drugs including biguanide, SGLT-2i, GLP-1RA, Thiazolidine, alpha-glucosidase inhibitor)	Yes	Yes	Yes
Combination therapy (3 or more drugs)	Yes	Yes	Yes
Prior treatment of glucose-lowering drugs	Yes	Yes	Yes
Polypharmacy: all drugs	Yes	Yes	Yes

JDS/JGS, Japan Diabetes Society/Japan Geriatrics Society; DPP-4i, dipeptidyl peptidase 4 inhibitor; SGLT2i, sodium glucose cotransporter 2 inhibitor; GLP-1RA, glucagon like peptide 1 receptor agonist.

Table S6. Additional baseline characteristics of adults aged ≥ 65 years with type 2 diabetes prescribed outpatient glucose lowering drugs

	Total (N=61,351)	Category I+II (N=56,130)	Category III (N=5,221)
No. of beds in medical institution ^a			
≤ 19	57,274 (93.4%)	52,571 (93.7%)	4,703 (90.1%)
20–99	1,672 (2.7%)	1,401 (2.5%)	271 (5.2%)
100–199	878 (1.4%)	802 (1.4%)	76 (1.5%)
≥ 200	1,565 (2.6%)	1,390 (2.5%)	175 (3.4%)
Comorbidities			
Diabetic retinopathy	12,735 (20.8%)	11,656 (20.8%)	1,079 (20.7%)
Diabetic neuropathy	3,791 (6.2%)	3,249 (5.8%)	542 (10.4%)
Hypertension	45,505 (74.2%)	40,942 (72.9%)	4,563 (87.4%)
Arthritis	2,177 (3.5%)	1,918 (3.4%)	259 (5.0%)
Urologic diseases or conditions	10,280 (16.8%)	8,773 (15.6%)	1,507 (28.9%)
Depression	3,750 (6.1%)	2,992 (5.3%)	758 (14.5%)
Multimorbidity			
Yes	55,793 (90.9%)	50,572 (90.1%)	5,221 (100.0%)
No. of comorbidities			
Mean (SD)	3.6 (1.8)	3.4 (1.5)	6.5 (1.7)
No. of comorbidities (category)			
< 4	32,348 (52.7%)	32,067 (57.1%)	281 (5.4%)
≥ 4	29,003 (47.3%)	24,063 (42.9%)	4,940 (94.6%)
Medical history of severe hypoglycemia			
Yes	236 (0.4%)	152 (0.3%)	84 (1.6%)

a) Patients may appear in more than one bed size category if glucose-lowering drugs were prescribed at multiple institutions.

SD, standard deviation.

Table S7. Glucose lowering treatment history, treatment complexity, and medication burden

	Total (N=61,351)	Category I+II (N=56,130)	Category III (N=5,221)
No. of glucose-lowering drugs classes			
Mean (SD)	1.7 (0.9)	1.7 (1.0)	1.6 (0.9)
No. of glucose-lowering drugs classes			
Single agent	33,101 (54.0%)	30,143 (53.7%)	2,958 (56.7%)
Combination therapy (2 drugs)	16,035 (26.1%)	14,629 (26.1%)	1,406 (26.9%)
Combination therapy (3 or more drugs)	12,215 (19.9%)	11,358 (20.2%)	857 (16.4%)
Prior treatment of glucose-lowering drugs			
Previously treated	48,804 (79.5%)	44,298 (78.9%)	4,506 (86.3%)
Untreated	12,547 (20.5%)	11,832 (21.1%)	715 (13.7%)
No. of drugs			
Mean (SD)	6.1 (3.4)	5.8 (3.3)	9.0 (3.9)
Polypharmacy: all drugs			
≤ 4 (No polypharmacy)	22,835 (37.2%)	22,289 (39.7%)	546 (10.5%)
5–9 (Polypharmacy)	29,232 (47.6%)	26,663 (47.5%)	2,569 (49.2%)
≥ 10 (Excessive polypharmacy)	9,284 (15.1%)	7,178 (12.8%)	2,106 (40.3%)
Polypharmacy: all drugs, oral glucose-lowering drugs			
≤ 4 (No polypharmacy), ≤ 1	16,459 (26.8%)	16,032 (28.6%)	427 (8.2%)
≤ 4 (No polypharmacy), 2	5,017 (8.2%)	4,914 (8.8%)	103 (2.0%)
≤ 4 (No polypharmacy), ≥ 3	1,359 (2.2%)	1,343 (2.4%)	16 (0.3%)
5–9 (Polypharmacy), ≤ 1	15,867 (25.9%)	14,161 (25.2%)	1,706 (32.7%)

5–9 (Polypharmacy), 2	7,901 (12.9%)	7,281 (13.0%)	620 (11.9%)
5–9 (Polypharmacy), ≥ 3	5,464 (8.9%)	5,221 (9.3%)	243 (4.7%)
≥ 10 (Excessive polypharmacy), ≤ 1	4,800 (7.8%)	3,538 (6.3%)	1,262 (24.2%)
≥ 10 (Excessive polypharmacy), 2	2,547 (4.2%)	2,000 (3.6%)	547 (10.5%)
≥ 10 (Excessive polypharmacy), ≥ 3	1,937 (3.2%)	1,640 (2.9%)	297 (5.7%)

SD, standard deviation.

Table S8. Patient characteristics for the analysis of HbA1c

	Total (N = 15,372)	Category I + II (N = 14,723)	Category III (N = 649)
Type of insurance			
Employees' Health Insurance Society	1,622 (10.6%)	1,605 (10.9%)	17 (2.6%)
National Health Insurance Society	8,594 (55.9%)	8,473 (57.5%)	121 (18.6%)
Latter-Stage Elderly Healthcare System	5,156 (33.5%)	4,645 (31.5%)	511 (78.7%)
Sex			
Male	8,908 (57.9%)	8,542 (58.0%)	366 (56.4%)
Female	6,464 (42.1%)	6,181 (42.0%)	283 (43.6%)
Age (years)			
Mean (SD)	72.8 (6.7)	72.5 (6.5)	80.0 (7.1)
Age group			
65–74	10,321 (67.1%)	10,180 (69.1%)	141 (21.7%)
≥ 75	5,051 (32.9%)	4,543 (30.9%)	508 (78.3%)
No. of beds in medical institution ^{a)}			
Not prescribed	1,938 (12.6%)	1,834 (12.5%)	104 (16.0%)
≤ 19	12,954 (84.3%)	12,446 (84.5%)	508 (78.3%)
20–99	193 (1.3%)	176 (1.2%)	17 (2.6%)
100–199	96 (0.6%)	94 (0.6%)	2 (0.3%)
≥ 200	200 (1.3%)	180 (1.2%)	20 (3.1%)
Comorbidities			
Dementia	441 (2.9%)	162 (1.1%)	279 (43.0%)
Mild	180 (1.2%)	162 (1.1%)	18 (2.8%)
Moderate to Severe	261 (1.7%)	0 (0.0%)	261 (40.2%)
Kidney disease	3,565 (23.2%)	3,188 (21.7%)	377 (58.1%)
Chronic kidney disease, except dialysis	3,548 (23.1%)	3,176 (21.6%)	372 (57.3%)
End-stage renal disease, dialysis	17 (0.1%)	12 (0.1%)	5 (0.8%)
Heart disease	2,632 (17.1%)	2,222 (15.1%)	410 (63.2%)
Myocardial infarction	547 (3.6%)	462 (3.1%)	85 (13.1%)
Congestive heart failure	2,416 (15.7%)	2,039 (13.8%)	377 (58.1%)
Cerebrovascular disease	3,494 (22.7%)	3,015 (20.5%)	479 (73.8%)
Chronic obstructive pulmonary disease	1,917 (12.5%)	1,655 (11.2%)	262 (40.4%)
Malignancy, except malignant neoplasm of skin	1,657 (10.8%)	1,446 (9.8%)	211 (32.5%)
Cirrhosis	127 (0.8%)	100 (0.7%)	27 (4.2%)

Fracture	935 (6.1%)	800 (5.4%)	135 (20.8%)
Peripheral Arterial Disease	1,088 (7.1%)	875 (5.9%)	213 (32.8%)
Diabetic retinopathy	3,351 (21.8%)	3,225 (21.9%)	126 (19.4%)
Diabetic neuropathy	715 (4.7%)	667 (4.5%)	48 (7.4%)
Hypertension	11,032 (71.8%)	10,457 (71.0%)	575 (88.6%)
Arthritis	492 (3.2%)	461 (3.1%)	31 (4.8%)
Urologic diseases or conditions	2,576 (16.8%)	2,374 (16.1%)	202 (31.1%)
Depression	700 (4.6%)	615 (4.2%)	85 (13.1%)
Multimorbidity			
Yes	13,965 (90.8%)	13,316 (90.4%)	649 (100.0%)
No. of comorbidities			
Mean (SD)	3.3 (1.6)	3.1 (1.4)	6.4 (1.6)
No. of comorbidities			
1	1,407 (9.2%)	1,407 (9.6%)	0 (0.0%)
2	4,068 (26.5%)	4,067 (27.6%)	1 (0.2%)
3	3,998 (26.0%)	3,964 (26.9%)	34 (5.2%)
4	2,864 (18.6%)	2,809 (19.1%)	55 (8.5%)
5	1,633 (10.6%)	1,562 (10.6%)	71 (10.9%)
6	850 (5.5%)	673 (4.6%)	177 (27.3%)
7	334 (2.2%)	185 (1.3%)	149 (23.0%)
≥ 8	218 (1.4%)	56 (0.4%)	162 (25.0%)
No. of comorbidities (category)			
< 4	9,473 (61.6%)	9,438 (64.1%)	35 (5.4%)
≥ 4	5,899 (38.4%)	5,285 (35.9%)	614 (94.6%)
Medical history of severe hypoglycemia			
Yes	26 (0.2%)	21 (0.1%)	5 (0.8%)
Glucose-lowering drugs			
None	1,938 (12.6%)	1,834 (12.5%)	104 (16.0%)
Biguanide	920 (6.0%)	899 (6.1%)	21 (3.2%)
DPP-4i	4,512 (29.4%)	4,285 (29.1%)	227 (35.0%)
GLP-1RA	20 (0.1%)	20 (0.1%)	0 (0.0%)
SGLT2i	304 (2.0%)	301 (2.0%)	3 (0.5%)
Thiazolidine	264 (1.7%)	258 (1.8%)	6 (0.9%)
Alpha-glucosidase inhibitor	456 (3.0%)	436 (3.0%)	20 (3.1%)
Glinide	84 (0.5%)	82 (0.6%)	2 (0.3%)
Sulfonylurea	350 (2.3%)	338 (2.3%)	12 (1.8%)

Basal insulin	40 (0.3%)	38 (0.3%)	2 (0.3%)
Other insulins	138 (0.9%)	127 (0.9%)	11 (1.7%)
Sulfonylurea plus biguanide	137 (0.9%)	133 (0.9%)	4 (0.6%)
Sulfonylurea plus DPP-4i	587 (3.8%)	553 (3.8%)	34 (5.2%)
Sulfonylurea plus SGLT2i	11 (0.1%)	11 (0.1%)	0 (0.0%)
Sulfonylurea plus other glucose-lowering drugs ^{b)}	125 (0.8%)	122 (0.8%)	3 (0.5%)
Basal insulin supported oral therapy	68 (0.4%)	61 (0.4%)	7 (1.1%)
Basal insulin plus GLP-1RA	12 (0.1%)	12 (0.1%)	0 (0.0%)
Biguanide plus DPP-4i	1,255 (8.2%)	1,208 (8.2%)	47 (7.2%)
Biguanide plus SGLT2i	55 (0.4%)	51 (0.3%)	4 (0.6%)
Biguanide plus other glucose-lowering drugs ^{b)}	189 (1.2%)	186 (1.3%)	3 (0.5%)
DPP-4i plus SGLT2i	189 (1.2%)	185 (1.3%)	4 (0.6%)
DPP-4i plus other glucose-lowering drugs ^{b)}	649 (4.2%)	629 (4.3%)	20 (3.1%)
SGLT2i plus other glucose-lowering drugs ^{b)}	18 (0.1%)	18 (0.1%)	0 (0.0%)
Combination therapy including other insulins (2 drugs)	233 (1.5%)	216 (1.5%)	17 (2.6%)
Other combination therapy including other glucose-lowering drugs (2 drugs) ^{b)}	86 (0.6%)	86 (0.6%)	0 (0.0%)
Combination therapy (3 or more drugs)	2,732 (17.8%)	2,634 (17.9%)	98 (15.1%)
No. of glucose-lowering drugs classes			
Mean (SD)	1.5 (1.1)	1.5 (1.1)	1.4 (1.0)
No. of glucose-lowering drugs classes			
None	1,938 (12.6%)	1,834 (12.5%)	104 (16.0%)
Single agent	7,088 (46.1%)	6,784 (46.1%)	304 (46.8%)
Combination therapy (2 drugs)	3,614 (23.5%)	3,471 (23.6%)	143 (22.0%)
Combination therapy (3 or more drugs)	2,732 (17.8%)	2,634 (17.9%)	98 (15.1%)
No. of drugs			
Mean (SD)	5.0 (3.1)	4.8 (3.0)	8.0 (3.6)
Polypharmacy: all drugs			
≤ 4 (No polypharmacy)	7,594 (49.4%)	7,494 (50.9%)	100 (15.4%)
5–9 (Polypharmacy)	6,483 (42.2%)	6,138 (41.7%)	345 (53.2%)
≥ 10 (Excessive polypharmacy)	1,295 (8.4%)	1,091 (7.4%)	204 (31.4%)

Polypharmacy: all drugs, oral glucose-lowering drugs			
≤ 4 (No polypharmacy), ≤ 1	5,686 (37.0%)	5,603 (38.1%)	83 (12.8%)
≤ 4 (No polypharmacy), 2	1,489 (9.7%)	1,473 (10.0%)	16 (2.5%)
≤ 4 (No polypharmacy), ≥ 3	419 (2.7%)	418 (2.8%)	1 (0.2%)
5–9 (Polypharmacy), ≤ 1	3,485 (22.7%)	3,249 (22.1%)	236 (36.4%)
5–9 (Polypharmacy), 2	1,710 (11.1%)	1,638 (11.1%)	72 (11.1%)
5–9 (Polypharmacy), ≥ 3	1,288 (8.4%)	1,251 (8.5%)	37 (5.7%)
≥ 10 (Excessive polypharmacy), ≤ 1	636 (4.1%)	507 (3.4%)	129 (19.9%)
≥ 10 (Excessive polypharmacy), 2	343 (2.2%)	298 (2.0%)	45 (6.9%)
≥ 10 (Excessive polypharmacy), ≥ 3	316 (2.1%)	286 (1.9%)	30 (4.6%)

a) Patients may appear in more than one bed -size category if glucose- lowering drugs were prescribed at multiple institutions.

b) Glinide, Thiazolidine, Alpha-glucosidase inhibitor, GLP-1RA

SD, standard deviation; DPP-4i, dipeptidyl peptidase 4 inhibitor; SGLT2i, sodium glucose cotransporter 2 inhibitor; GLP-1RA, glucagon like peptide 1 receptor agonist.