

Supplemental material

Multimorbidity, polypharmacy, severe hypoglycemia, and glycemic control in patients using glucose-lowering drugs for type 2 diabetes: A retrospective cohort study using health insurance claims in Japan

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Supplemental table S1 : Definition of diseases and drugs

Definition of diabetes mellitus

Type 2 diabetes mellitus

Among the patients who received outpatient prescriptions for glucose-lowering drugs, those to whom any of the following ICD-10 codes and prescribed glucose-lowering drugs applied from April 2017 to February 2020.

E11, E12, E13, or E14

Type 1 diabetes mellitus

Patients for whom any of the following ICD-10 codes applied during the baseline period, including the index month from April 2017 to February 2020.

E10

Definition of drug

Glucose-lowering drugs: ATC codes as A10C, A10H, A10J, A10K, A10L, A10M, A10N, A10P, and A10S

*In case glucose-lowering drugs were prescribed to any patients for whom the disease name "type 2 diabetes" applied.

Definitions of disease

Dementia

Patients for whom any of the following ICD-10 codes applied during the baseline period.

F00, F01, F02, F03, F04, F05, F060, G30, G310, G311, G318, G94, R418

End-stage renal disease, dialysis

Patients for whom any of the following receipt codes applied during the baseline period.

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

Patients for whom any of the following ICD-10 codes applied and "ESRD, dialysis" did not apply for the baseline period.

E112, E132, E142, I12, I13, I150, I151, N00-N08, N11, N12, N14, N15, N16, N18, N19, N25, N26, N27, N28, N391, N392, E851, D593, B52, Q60, Q61, Q62, Q63

Myocardial infarction

Patients for whom any of the following ICD-10 codes applied during the baseline period.

I21, I22, I252

Congestive heart failure

Patients for whom any of the following ICD-10 codes applied during the baseline period.

I099, I110, I130, I132, I255, I420, I425, I426, I427, I428, I429, I43, I50, P290

Cerebrovascular disease

Patients for whom any of the following ICD-10 codes applied during the baseline period.

G45, G46, H340, I60, I61, I62, I63, I64, I65, I66, I67, I68, I69

Chronic obstructive pulmonary disease

Patients for whom any of the following ICD-10 codes applied during the baseline period.

J40, J41, J42, J43, J44, J47

Malignancy, excluding malignant skin neoplasm

Patients for whom any of the following ICD-10 codes applied during the baseline period.

C00–C14, C15–26, C30–C39, C40–C41, C43, C45–C49, C50, C51–C58, C60–C63, C64–C68, C69–C72, C73–C75, C76, C81, C82, C83, C84, C85, C88, C90, C91, C92, C93, C94, C95, C96, C97

Cirrhosis

Patients for whom any of the following ICD-10 codes applied during the baseline period.

K703, K743, K744, K745, K746

Diabetic retinopathy

Patients for whom any of the following ICD-10 codes applied during the baseline period.

E113, E143, H360

Diabetic neuropathy

Patients for whom any of the following ICD-10 codes applied during the baseline period.

E114, E144

Hypertension

Patients for whom any of the following ICD-10 codes applied during the baseline period.

I10, I11, I12, I13, I15, I16

Arthritis

Patients for whom any of the following ICD-10 codes applied during the baseline period.

M05, M06, M120, M352, M45, M461, M468, M469, M498, M353

Urologic diseases or conditions

Patients for whom any of the following ICD-10 codes applied during the baseline period.

N301, N320, N393, N394, N40, R32

Patients for whom any of the following disease name code applied during the baseline period.

8843031, 8844583

Depression

Patients for whom any of the following ICD-10 codes applied during the baseline period.

F32, F33

Fracture

Patients for whom any of the following ICD-10 codes applied during the baseline period.

S02, S12, S22, S32, S42, S52, S62, S72, S82, S92, T02, T08, T10, T12, M80, T142

Definition of hypoglycemia

Main analysis

Patients for whom any of the following ICD-10 codes applied, and who were prescribed either 20%, 40% or 50% glucose infusion or glucagon infusion on the same insurance claim form.

E110, E120, E130, E140, E15, E160, E161, E162.

Sensitive analysis

Patients for whom any of the following ICD-10 codes applied, and who prescribed 50% glucose infusion or glucagon infusion on the same insurance claim form.

E110, E120, E130, E140, E15, E160, E161, E162.

Supplemental table S2 : Patient characteristics stratified by glucose-lowering drugs

	Biguanide N=6,936	DPP-4i N=29,893	SGLT-2i N=3,362	Glinide N=504	SU N=2,434	GLP-1RA, thiazolidine, α glucosidase inhibitor ^a N=4,183	Insulin ^b N=1,865	SU combination ^c N=5,976	Glinide combination ^d N=1,065	BOT ^e N=699	Basal insulin +GLP-1RA N=66	Other types of insulin combination ^f N=2,090	DPP-4i combination ^g N=12,572	Other 2-drug combination ^h N=1,910	3-or-more-drug combination N=20,266
Sex, n (%)															
Male	4,282 (61.7)	17,123 (57.3)	2,056 (61.2)	337 (66.9)	1,482 (60.9)	2,444 (58.4)	1,147 (61.5)	3,684 (61.6)	624 (59.1)	411 (58.8)	36 (54.5)	1,281 (61.3)	7,577 (60.3)	1,172 (61.4)	12,636 (62.4)
Female	2,654 (38.3)	12,770 (42.7)	1,306 (38.8)	167 (33.1)	952 (39.1)	1,739 (41.6)	718 (38.5)	2,292 (38.4)	431 (40.9)	288 (41.2)	30 (45.5)	809 (38.7)	4,995 (39.7)	738 (38.6)	7,620 (37.6)
Age, years	62.3±12.4	69.9±12.1	59.8±12.9	67.9±11.6	70.2±11.8	69.6±12.2	66.9±13.9	69.5±11.0	69.8±11.0	68.6±13.8	66.9±12.5	66.2±12.2	67.0±11.9	61.9±12.6	65.2±11.2
Age category, n (%)															
18–44	624 (9.0)	877 (2.9)	429 (12.8)	21 (4.2)	54 (2.2)	131 (3.1)	136 (7.3)	131 (2.2)	23 (2.2)	43 (6.2)	4 (6.1)	126 (6.0)	496 (3.9)	184 (9.6)	909 (4.5)
45–64	2,754 (39.7)	7,253 (24.3)	1,522 (45.3)	133 (26.4)	586 (24.1)	1,015 (24.3)	541 (29.0)	1,467 (24.5)	254 (24.1)	180 (25.8)	20 (30.3)	627 (30.0)	4,011 (31.9)	767 (40.2)	7,132 (35.2)
65–74	2,602 (37.5)	11,127 (37.2)	1,063 (31.6)	209 (41.5)	969 (39.8)	1,566 (37.4)	646 (34.6)	2,500 (41.8)	436 (41.3)	238 (34.0)	20 (30.3)	839 (40.1)	4,691 (37.3)	685 (35.9)	8,398 (41.5)
≥75	956 (13.8)	10,636 (35.6)	348 (10.4)	141 (28.0)	825 (33.9)	1,471 (35.2)	542 (29.1)	1,878 (31.4)	342 (32.4)	238 (34.0)	22 (33.3)	498 (23.8)	3,374 (26.8)	274 (14.3)	3,817 (18.8)
Type of insurance, n (%)															
SHI	1,950 (28.1)	4,756 (15.9)	1,124 (33.4)	88 (17.5)	335 (13.8)	689 (16.0)	293 (15.7)	873 (14.6)	163 (15.5)	91 (13.0)	11 (16.7)	336 (16.1)	2,534 (20.2)	531 (27.8)	4,548 (22.5)
NHI	4,007 (57.8)	14,329 (47.9)	1,874 (55.7)	271 (53.8)	1,260 (51.8)	2,015 (48.2)	1,004 (53.8)	3,196 (53.5)	543 (51.5)	362 (51.8)	33 (50.0)	1,231 (58.9)	6,605 (52.5)	1,100 (57.6)	11,792 (58.2)
LSEHS	979 (14.1)	10,808 (36.2)	364 (10.8)	145 (28.8)	839 (34.5)	1,489 (35.8)	568 (30.5)	1,907 (31.9)	349 (33.1)	246 (35.2)	22 (33.3)	523 (25.0)	3,433 (27.3)	279 (14.6)	3,916 (19.3)
No. of beds in medical institution ⁱ , n (%)															
≤19	6,593 (95.1)	28,267 (94.6)	3,249 (96.6)	476 (94.4)	2,290 (94.1)	3,908 (93.4)	1,560 (83.6)	5,662 (94.7)	988 (93.6)	625 (89.4)	56 (84.8)	1,862 (89.1)	11,841 (94.2)	1,797 (94.1)	18,931 (93.5)
20–99	106 (1.5)	540 (1.8)	19 (0.6)	14 (2.8)	77 (3.2)	110 (2.6)	75 (4.0)	93 (1.6)	17 (1.6)	35 (5.0)	3 (4.5)	83 (4.0)	251 (2.0)	37 (1.9)	468 (2.3)
100–199	90 (1.3)	428 (1.4)	27 (0.8)	9 (1.8)	37 (1.5)	48 (1.1)	72 (3.9)	86 (1.4)	10 (0.9)	11 (1.6)	4 (6.1)	36 (1.7)	178 (1.4)	32 (1.7)	294 (1.5)
≥200	148 (2.1)	659 (2.2)	67 (2.0)	5 (1.0)	30 (1.2)	117 (2.8)	159 (8.5)	135 (2.3)	41 (3.9)	33 (4.7)	3 (4.5)	130 (6.2)	302 (2.4)	46 (2.4)	603 (3.0)
Comorbidities, n (%)															
Dementia	132 (1.9)	1,928 (6.4)	50 (1.5)	14 (2.8)	126 (5.2)	182 (4.4)	125 (6.7)	293 (4.9)	57 (5.4)	71 (10.2)	3 (4.5)	75 (3.6)	566 (4.5)	32 (1.7)	557 (2.7)
ESRD, dialysis	1 (0.0)	622 (2.1)	3 (0.1)	22 (4.4)	5 (0.2)	87 (2.1)	183 (9.8)	13 (0.2)	62 (5.9)	27 (3.9)	2 (3.0)	78 (3.7)	99 (0.8)	2 (0.1)	99 (0.5)
CKD, excluding dialysis	973 (14.0)	6,006 (20.1)	551 (16.4)	103 (20.4)	441 (18.1)	849 (20.3)	540 (29.0)	1,499 (25.1)	291 (27.6)	251 (35.9)	25 (37.9)	761 (36.4)	2,843 (22.6)	411 (21.5)	5,984 (29.5)
Myocardial infarction	162 (2.3)	1,199 (4.0)	170 (5.1)	19 (3.8)	66 (2.7)	154 (3.7)	106 (5.7)	269 (4.5)	51 (4.8)	40 (5.7)	4 (6.1)	124 (5.9)	529 (4.2)	78 (4.1)	1,011 (5.0)
CHF	662 (9.5)	6,202 (20.7)	614 (18.3)	98 (19.4)	380 (15.6)	776 (18.6)	467 (25.0)	975 (16.3)	244 (23.1)	173 (24.7)	14 (21.2)	441 (21.1)	2,156 (17.1)	223 (11.7)	3,099 (15.3)
CBVD	985 (14.2)	6,842 (22.9)	446 (13.3)	102 (20.2)	577 (23.7)	983 (23.5)	481 (25.8)	1,393 (23.3)	285 (27.0)	219 (31.3)	21 (31.8)	494 (23.6)	2,729 (21.7)	276 (14.5)	4,172 (20.6)
COPD	717 (10.3)	4,121 (13.8)	410 (12.2)	67 (13.3)	302 (12.4)	592 (14.2)	262 (14.0)	709 (11.9)	145 (13.7)	100 (14.3)	12 (18.2)	296 (14.2)	1,370 (10.9)	180 (9.4)	2,318 (11.4)
Malignancy, excluding malignant skin neoplasm	565 (8.1)	3,629 (12.1)	203 (6.0)	93 (18.5)	280 (11.5)	491 (11.7)	368 (19.7)	680 (11.4)	152 (14.4)	109 (15.6)	3 (4.5)	319 (15.3)	1,229 (9.8)	133 (7.0)	1,785 (8.8)
Cirrhosis	46 (0.7)	419 (1.4)	47 (1.4)	10 (2.0)	33 (1.4)	65 (1.6)	97 (5.2)	98 (1.6)	20 (1.9)	17 (2.4)	1 (1.5)	85 (4.1)	138 (1.1)	25 (1.3)	260 (1.3)
Diabetic retinopathy	817 (11.8)	3,213 (10.7)	184 (5.5)	98 (19.4)	372 (15.3)	581 (13.9)	652 (35.0)	1,354 (22.7)	288 (27.3)	252 (36.1)	29 (43.9)	992 (47.5)	2,507 (19.9)	412 (21.6)	7,147 (35.3)
Diabetic neuropathy	175 (2.5)	790 (2.6)	39 (1.2)	21 (4.2)	99 (4.1)	146 (3.5)	269 (14.4)	393 (6.6)	84 (8.0)	110 (15.7)	16 (24.2)	354 (16.9)	591 (4.7)	97 (5.1)	2,103 (10.4)
Hypertension	4,021 (58.0)	20,708 (69.3)	2,186 (65.0)	312 (61.9)	1,698 (69.8)	3,001 (71.7)	1,159 (62.1)	4,138 (69.2)	747 (70.8)	445 (63.7)	45 (68.2)	1,362 (65.2)	8,531 (67.9)	1,232 (64.5)	13,858 (68.4)
Arthritis	128 (1.8)	1,060 (3.5)	73 (2.2)	33 (6.5)	72 (3.0)	143 (3.4)	70 (3.8)	143 (2.4)	57 (5.4)	32 (4.6)	3 (4.5)	84 (4.0)	333 (2.6)	37 (1.9)	498 (2.5)
Urologic diseases or conditions	686 (9.9)	4,258 (14.2)	273 (8.1)	63 (12.5)	356 (14.6)	657 (15.7)	225 (12.1)	824 (13.8)	152 (14.4)	96 (13.7)	9 (13.6)	237 (11.3)	1,552 (12.3)	181 (9.5)	2,252 (11.1)
Depression	428 (6.2)	2,101 (7.0)	288 (8.6)	43 (8.5)	141 (5.8)	270 (6.5)	147 (7.9)	314 (5.3)	71 (6.7)	60 (8.6)	4 (6.1)	139 (6.7)	740 (5.9)	112 (5.9)	1,118 (5.5)
Fracture	335 (4.8)	2,521 (8.4)	158 (4.7)	47 (9.3)	190 (7.8)	378 (9.0)	186 (10.0)	463 (7.7)	83 (7.9)	65 (9.3)	8 (12.1)	213 (10.2)	892 (7.1)	122 (6.4)	1,384 (6.8)

Supplemental table S2 : Continued.

	Biguanide N=6,936	DPP-4i N=29,893	SGLT-2i N=3,362	Glinide N=504	SU N=2,434	GLP-1RA, α glucosidase inhibitor ^a N=4,183	Insulin ^b N=1,865	SU combination ^c N=5,976	Glinide combination ^d N=1,055	BOT ^e N=699	Basal insulin +GLP-1RA N=66	Other types of insulin combination ^f N=2,090	DPP-4i combination ^g N=12,572	Other 2-drug combination ^h N=1,910	3-or-more-drug combination ⁱ N=20,256
Multimorbidity	5,244 (75.6)	25,382 (84.9)	2,626 (78.1)	421 (83.5)	2,068 (85.0)	3,676 (87.9)	1,558 (83.5)	5,233 (87.6)	954 (90.4)	619 (88.6)	56 (84.8)	1,868 (89.4)	10,777 (85.7)	1,606 (84.1)	18,108 (89.4)
No. of comorbidities	2.6±1.4	3.2±1.7	2.7±1.5	3.3±1.7	3.1±1.6	3.2±1.6	3.9±2.1	3.3±1.6	3.6±1.8	4.0±2.0	4.0±1.9	3.9±1.9	3.1±1.6	2.9±1.4	3.4±1.6
Total no. of comorbidities, n (%)															
1	1,692 (24.4)	4,511 (15.1)	736 (21.9)	83 (16.5)	366 (15.0)	507 (12.1)	307 (16.5)	743 (12.4)	101 (9.6)	80 (11.4)	10 (15.2)	222 (10.6)	1,795 (14.3)	304 (15.9)	2,148 (10.6)
2	2,248 (32.4)	7,558 (25.3)	1,025 (30.5)	109 (21.6)	650 (26.7)	1,060 (25.3)	251 (13.5)	1,452 (24.3)	217 (20.6)	108 (15.5)	5 (7.6)	314 (15.0)	3,290 (26.2)	541 (28.3)	4,687 (23.1)
3	1,474 (21.3)	6,669 (22.3)	756 (22.5)	113 (22.4)	566 (23.3)	1,039 (24.8)	292 (15.7)	1,475 (24.7)	206 (19.5)	129 (18.5)	8 (12.1)	411 (19.7)	3,060 (24.3)	546 (28.6)	5,069 (25.0)
4	847 (12.2)	4,964 (16.6)	460 (13.7)	72 (14.3)	402 (16.5)	720 (17.2)	316 (16.9)	1,059 (17.7)	216 (20.5)	120 (17.2)	18 (27.3)	406 (19.4)	2,067 (16.4)	303 (15.9)	3,937 (19.4)
5	404 (5.8)	3,128 (10.5)	235 (7.0)	76 (15.1)	240 (9.9)	446 (10.7)	288 (15.4)	632 (10.6)	168 (15.9)	102 (14.6)	11 (16.7)	323 (15.5)	1,275 (10.1)	122 (6.4)	2,324 (11.5)
6	188 (2.7)	1,726 (5.8)	87 (2.6)	29 (5.8)	117 (4.8)	258 (6.2)	201 (10.8)	367 (6.1)	87 (8.2)	79 (11.3)	6 (9.1)	203 (9.7)	647 (5.1)	58 (3.0)	1,249 (6.2)
7	52 (0.7)	841 (2.8)	42 (1.2)	11 (2.2)	59 (2.4)	106 (2.5)	120 (6.4)	157 (2.6)	29 (2.7)	45 (6.4)	6 (9.1)	126 (6.0)	259 (2.1)	24 (1.3)	549 (2.7)
≥8	31 (0.4)	496 (1.7)	21 (0.6)	11 (2.2)	34 (1.4)	47 (1.1)	90 (4.8)	91 (1.5)	31 (2.9)	36 (5.2)	2 (3.0)	85 (4.1)	179 (1.4)	12 (0.6)	293 (1.4)
Prior severe hypoglycemia, n (%)	3 (0.0)	72 (0.2)	1 (0.0)	1 (0.2)	4 (0.2)	16 (0.4)	44 (2.4)	17 (0.3)	9 (0.9)	7 (1.0)	0 (0.0)	39 (1.9)	25 (0.2)	3 (0.2)	69 (0.3)
No. of glucose-lowering drug classes	1.0±0.0	1.0±0.0	1.0±0.0	1.0±0.0	1.0±0.0	1.0±0.0	1.0±0.0	2.0±0.0	2.0±0.0	2.0±0.0	2.0±0.0	2.0±0.0	2.0±0.0	2.0±0.0	3.4±0.6
Prior treatment with glucose-lowering drugs, n (%)															
Previously treated	3,645 (52.6)	18,511 (61.9)	1,051 (31.3)	372 (73.8)	1,945 (79.9)	3,145 (75.2)	1,478 (79.2)	5,618 (94.0)	999 (94.7)	614 (87.8)	62 (93.9)	1,959 (93.7)	11,383 (90.5)	1,648 (86.3)	19,655 (97.0)
Untreated	3,291 (47.4)	11,382 (38.1)	2,311 (68.7)	132 (26.2)	489 (20.1)	1,038 (24.8)	387 (20.8)	358 (6.0)	56 (5.3)	85 (12.2)	4 (6.1)	131 (6.3)	1,189 (9.5)	262 (13.7)	601 (3.0)
No. of drugs	4.2±3.0	5.3±3.5	4.9±3.5	5.3±3.9	5.1±3.2	5.4±3.3	4.9±4.4	6.0±3.2	6.7±3.9	5.6±3.9	5.0±4.2	5.2±4.2	5.7±3.3	5.4±3.0	6.8±3.2
No. of drugs, n (%)															
≤4 (no polypharmacy)	4,407 (63.5)	14,707 (49.2)	1,891 (56.2)	257 (51.0)	1,201 (49.3)	1,966 (47.0)	994 (53.3)	2,321 (38.8)	347 (32.9)	331 (47.4)	37 (56.1)	1,050 (50.2)	5,364 (42.7)	882 (46.2)	5,201 (25.7)
5-9 (polypharmacy)	2,118 (30.5)	11,886 (39.1)	1,137 (33.8)	178 (35.3)	1,016 (41.7)	1,744 (41.7)	590 (31.6)	2,844 (47.6)	486 (46.1)	253 (36.2)	18 (27.3)	728 (34.8)	5,613 (44.6)	838 (43.9)	11,500 (56.8)
≥10 (excessive polypharmacy)	411 (5.9)	3,500 (11.7)	334 (9.9)	69 (13.7)	217 (8.9)	473 (11.3)	281 (15.1)	811 (13.6)	222 (21.0)	115 (16.5)	11 (16.7)	312 (14.9)	1,595 (12.7)	190 (9.9)	3,555 (17.6)

Data presented as mean±SD unless otherwise stated.

- a. GLP-1RA (N=221), thiazolidine (N=1,290), α glucosidase inhibitor (N=2,672)
- b. Basal insulin (N=513), other types of insulin (N=1,352).
- c. SU+biguanide (N=864), DPP-4i (N=4,058), SGLT-2i (N=122), glinide, GLP-1RA, thiazolidine, α glucosidase inhibitor (N=932)
- d. Glinide+biguanide (N=106), DPP-4i (N=662), SGLT-2i (N=14), others (GLP-1RA or thiazolidine or α glucosidase inhibitor)(N=273)
- e. Basal insulin+biguanide, DPP-4i, SGLT-2i, glinide, SU, thiazolidine, α glucosidase inhibitor
- f. Other types of insulin+biguanide, DPP-4i, SGLT-2i, glinide, SU, GLP-1RA, thiazolidine, α glucosidase inhibitor, basal insulin
- g. DPP-4i+biguanide (N=7,947), SGLT-2i (N=1,167), others (GLP-1RA or thiazolidine or α glucosidase inhibitor)(N=3,458)
- h. 2 drugs including biguanide, SGLT-2i, GLP-1RA, thiazolidine, α glucosidase inhibitor
- i. Some overlap in counting is acceptable.

BOT, basal insulin-supported oral therapy; CBVD, cerebrovascular disease; CKD, chronic kidney disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DPP-4i, dipeptidyl peptidase-4 inhibitor; ESRD, end-stage renal disease; GLP-1RA, glucagon-like peptide-1 receptor agonist; LSEHS, latter-stage elderly health care system; NHI, national health insurance; SGLT-2i, sodium glucose cotransporter-2 inhibitor; SHI, society-managed employment-based health insurance association; SD, standard deviation; SU, sulfonylurea.

Supplemental table S3 : Crude incidence rates for severe hypoglycemia

	<i>N</i>	Crude incidence rate (95%CI)
Overall	93,801	5.85 (5.37, 6.37)
Sex		
Male	56,292	5.62 (5.01, 6.29)
Female	37,509	6.19 (5.41, 7.05)
Age, years		
18–29	335	9.69 (1.95, 28.30)
30–39	1,558	7.99 (4.12, 13.95)
40–49	6,445	7.46 (5.48, 9.93)
50–59	12,557	2.70 (1.86, 3.79)
60–69	38,148	4.15 (3.52, 4.86)
70–79	18,172	5.42 (4.40, 6.62)
≥80	16,586	11.77 (10.15, 13.57)
Type of insurance		
SHI	18,302	1.75 (1.19, 2.48)
NHI	49,622	5.06 (4.44, 5.73)
LSEHS	25,877	10.27 (9.06, 11.60)
No. of beds in medical institution ^a		
≤19	88,105	5.63 (5.14, 6.16)
20–99	1,928	13.22 (8.55, 19.52)
100–199	1,362	4.56 (1.66, 9.92)
≥200	2,478	8.82 (5.46, 13.49)
Comorbidities		
Dementia	4,211	18.12 (14.18, 22.82)
ESRD, dialysis	1,305	110.31 (92.55, 130.49)
CKD, excluding dialysis	21,528	8.77 (7.55, 10.14)
Myocardial infarction	3,982	8.56 (5.89, 12.02)
CHF	16,524	14.29 (12.50, 16.27)
CBVD	20,005	10.84 (9.43, 12.41)
COPD	11,601	9.45 (7.74, 11.43)
Malignancy, excluding malignant skin neoplasm	10,039	12.26 (10.15, 14.68)
Cirrhosis	1,361	13.10 (7.63, 20.98)
Diabetic retinopathy	18,898	11.88 (10.36, 13.56)
Diabetic neuropathy	5,287	17.61 (14.18, 21.62)
Hypertension	63,443	7.31 (6.65, 8.02)
Arthritis	2,766	10.38 (6.90, 15.01)
Urologic diseases or conditions	11,821	7.55 (6.05, 9.31)
Depression	5,976	6.92 (4.94, 9.42)
Fracture	7,045	13.93 (11.27, 17.02)
Multimorbidity		
No	13,605	1.13 (0.63, 1.86)
Yes	80,196	6.65 (6.09, 7.25)
No. of comorbidities		
1	13,605	1.13 (0.63, 1.86)
2	23,515	1.56 (1.09, 2.16)
3	21,813	4.25 (3.42, 5.22)
4	15,907	5.78 (4.65, 7.11)
5	9,774	11.28 (9.24, 13.63)
6	5,302	15.08 (11.90, 18.85)
7	2,426	23.35 (17.54, 30.47)
≥8	1,459	48.03 (37.14, 61.11)
Prior severe hypoglycemia		
No	93,491	4.59 (4.16, 5.05)
Yes	310	401.50 (332.05, 481.19)

Supplemental table S3 : Continued.

	N	Crude incidence rate (95%CI)
Glucose-lowering drugs		
Biguanide	6,936	0.88 (0.32, 1.92)
DPP-4i	29,893	3.47 (2.82, 4.21)
SGLT-2i	3,362	0.30 (0.00, 1.69)
Glinide	504	24.37 (12.58, 42.57)
SU	2,434	5.49 (2.92, 9.38)
GLP-1RA, thiazolidine, α glucosidase inhibitor	4,183	3.42 (1.87, 5.74)
GLP-1RA	221	4.69 (0.06, 26.09)
Thiazolidine	1,290	0.79 (0.01, 4.39)
α glucosidase inhibitor	2,672	4.60 (2.37, 8.03)
Insulin ^b	1,865	52.47 (42.35, 64.28)
Basal insulin	513	39.50 (23.77, 61.69)
Other types of insulin	1,352	57.30 (44.99, 71.94)
SU combination ^c	5,976	5.99 (4.17, 8.33)
SU+biguanide	864	3.54 (0.71, 10.35)
SU+DPP-4i	4,058	5.81 (3.68, 8.71)
SU+SGLT-2i	122	8.35 (0.11, 46.45)
SU+other glucose-lowering drugs ^d	932	8.76 (3.77, 17.26)
Glinide combination ^e	1,055	28.19 (18.88, 40.49)
BOT ^f	699	17.86 (9.22, 31.20)
Basal insulin+GLP-1RA	66	0.00 (0.00, 57.52)
Biguanide+DPP-4i	7,947	2.18 (1.27, 3.49)
Biguanide+SGLT-2i	568	1.81 (0.02, 10.06)
Biguanide+other glucose-lowering drugs ^d	1,106	0.92 (0.01, 5.12)
DPP-4i combination ^g	12,572	2.44 (1.64, 3.48)
DPP-4i+SGLT-2i	1,167	3.53 (0.95, 9.04)
DPP-4i+other glucose-lowering drugs ^d	4,120	9.17 (6.46, 12.64)
SGLT-2i+other glucose-lowering drugs ^d	143	0.00 (0.00, 26.61)
Other types of insulin combination ^h	2,090	32.12 (24.79, 40.94)
Other 2-drug combination ⁱ	1,910	1.61 (0.32, 4.69)
Other glucose-lowering drug ^d combination	486	4.20 (0.47, 15.15)
3-or-more-drug combination	20,256	6.14 (5.10, 7.33)
Classes of glucose-lowering drugs		
Monotherapy	49,177	5.01 (4.39, 5.68)
2-drug combination therapy	24,368	7.31 (6.26, 8.48)
3-or-more-drug combination therapy	20,256	6.14 (5.10, 7.33)
Prior treatment with glucose-lowering drugs		
Previously treated	72,085	6.91 (6.31, 7.55)
Untreated	21,716	2.32 (1.71, 3.06)
No. of drugs		
≤ 4 (no polypharmacy)	40,956	2.69 (2.21, 3.25)
5–9 (polypharmacy)	40,749	5.65 (4.93, 6.43)
≥ 10 (excessive polypharmacy)	12,096	17.43 (15.12, 20.00)

The CI for incidence rate was calculated using the Byar's method.

Incidence rate was calculated as the number of occurrences of severe hypoglycemia/1000 person-years.

a. Some overlap in counting is acceptable.

b. Basal insulin, other types of insulin

c. SU+biguanide, DPP-4i, SGLT-2i, glinide, GLP-1RA, thiazolidine, α glucosidase inhibitor

d. Glinide, GLP-1RA, thiazolidine, α glucosidase inhibitor

e. Glinide+biguanide, DPP-4i, SGLT-2i, GLP-1RA, thiazolidine, α glucosidase inhibitor

f. Basal insulin+biguanide, DPP-4i, SGLT-2i, glinide, SU, thiazolidine, α glucosidase inhibitor

g. DPP-4i+biguanide, SGLT-2i, GLP-1RA, thiazolidine, α glucosidase inhibitor

h. Other types of insulin+biguanide, DPP-4i, SGLT-2i, glinide, SU, GLP-1RA, thiazolidine, α glucosidase inhibitor, basal insulin

i. 2 drugs including biguanide, SGLT-2i, GLP-1RA, thiazolidine, α glucosidase inhibitor

BOT, basal insulin supported oral therapy; CBVD, cerebrovascular disease; CHF, congestive heart failure; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DPP-4i, dipeptidyl peptidase-4 inhibitor; ESRD, end-stage renal disease; GLP-1RA, glucagon-like peptide-1 receptor agonist; LSEHS, latter-stage elderly health care system; NHI, national health insurance; SGLT-2i, sodium glucose cotransporter-2 inhibitor; SHI, society-managed employment-based health insurance association; SU, sulfonylurea.

Supplemental table S4: Factors affecting the incidence rate of severe hypoglycemia

Variable	Univariable analysis			Multivariable analysis		
	N	Crude IR (No./1000 person-years)	Unadjusted IRR (95%CI)	N	Crude IR (No./1000 person-years)	Adjusted IRR (95%CI)
Sex						
Male	56,292	5.62 (309/54.95)	1.00	56,256	5.63 (309/54.92)	1.00
Female	37,509	6.19 (227/36.65)	1.12 (0.88, 1.42)	37,479	6.20 (227/36.62)	1.05 (0.83, 1.34)
Age (years)						
18–29	335	9.69 (3/0.31)	3.64 (0.63, 20.91)	334	9.72 (3/0.31)	12.28 (2.96, 50.92)
30–39	1,558	7.99 (12/1.50)	2.93 (1.18, 7.24)	1,556	8.00 (12/1.50)	2.23 (0.72, 6.92)
40–49	6,445	7.46 (47/6.30)	2.74 (1.55, 4.84)	6,444	7.47 (47/6.30)	3.26 (1.76, 6.04)
50–59	12,557	2.70 (33/12.22)	1.00	12,546	2.70 (33/12.21)	1.00
60–69	38,148	4.15 (155/37.33)	1.56 (1.00, 2.44)	38,124	4.15 (155/37.31)	1.24 (0.75, 2.04)
70–79	18,172	5.42 (97/17.88)	2.07 (1.28, 3.33)	18,152	5.43 (97/17.86)	2.03 (1.20, 3.42)
≥80	16,586	11.77 (189/16.06)	4.87 (3.07, 7.73)	16,579	11.78 (189/16.05)	4.03 (2.38, 6.80)
Comorbidities						
Dementia						
No	89,590	5.30 (464/87.63)	1.00	89,527	5.30 (464/87.57)	1.00
Yes	4,211	18.12 (72/3.97)	3.89 (2.46, 6.16)	4,208	18.13 (72/3.97)	1.88 (1.30, 2.70)
ESRD, dialysis						
No	92,496	4.43 (400/90.37)	1.00	92,432	4.43 (400/90.31)	1.00
Yes	1,305	110.31 (136/1.23)	26.00 (15.62, 43.29)	1,303	110.49 (136/1.23)	10.35 (6.46, 16.58)
CKD, excluding dialysis						
No	72,273	4.98 (352/70.63)	1.00	72,232	4.99 (352/70.59)	1.00
Yes	21,528	8.77 (184/20.97)	1.84 (1.42, 2.39)	21,503	8.78 (184/20.95)	1.61 (1.26, 2.06)
Myocardial infarction						
No	89,819	5.73 (503/87.75)	1.00	89,757	5.74 (503/87.69)	1.00
Yes	3,982	8.56 (33/3.85)	1.58 (0.92, 2.72)	3,978	8.57 (33/3.85)	0.66 (0.39, 1.11)
CHF						
No	77,277	4.07 (308/75.65)	1.00	77,225	4.07 (308/75.60)	1.00
Yes	16,524	14.29 (228/15.95)	3.80 (2.93, 4.91)	16,510	14.30 (228/15.94)	1.36 (1.04, 1.78)
CBVD						
No	73,796	4.50 (325/72.14)	1.00	73,751	4.51 (325/72.10)	1.00
Yes	20,005	10.84 (211/19.46)	2.50 (1.94, 3.23)	19,984	10.85 (211/19.44)	1.28 (0.99, 1.65)
COPD						
No	82,200	5.35 (430/80.39)	1.00	82,146	5.35 (430/80.34)	1.00
Yes	11,601	9.45 (106/11.21)	1.92 (1.38, 2.66)	11,589	9.46 (106/11.20)	1.07 (0.79, 1.45)
Malignancy, excluding malignant skin neoplasm						
No	83,762	5.10 (418/81.98)	1.00	83,699	5.10 (418/81.92)	1.00
Yes	10,039	12.26 (118/9.63)	2.65 (1.90, 3.69)	10,036	12.26 (118/9.62)	2.10 (1.58, 2.78)
Cirrhosis						
No	92,440	5.75 (519/90.30)	1.00	92,375	5.75 (519/90.24)	1.00
Yes	1,361	13.10 (17/1.30)	3.11 (1.30, 7.43)	1,360	13.11 (17/1.30)	1.88 (1.00, 3.54)
Diabetic retinopathy						
No	74,903	4.32 (316/73.09)	1.00	74,866	4.33 (316/73.05)	1.00
Yes	18,898	11.88 (220/18.51)	2.71 (2.10, 3.49)	18,869	11.90 (220/18.49)	1.27 (0.98, 1.65)
Diabetic neuropathy						
No	88,514	5.15 (445/86.43)	1.00	88,464	5.15 (445/86.39)	1.00
Yes	5,287	17.61 (91/5.17)	3.59 (2.39, 5.39)	5,271	17.66 (91/5.15)	1.01 (0.70, 1.46)
Hypertension						
No	30,358	2.80 (83/29.63)	1.00	30,337	2.80 (83/29.61)	1.00
Yes	63,443	7.31 (453/61.97)	2.70 (2.03, 3.60)	63,398	7.32 (453/61.93)	1.26 (0.92, 1.72)
Arthritis						
No	91,035	5.71 (508/88.91)	1.00	90,972	5.72 (508/88.84)	1.00
Yes	2,766	10.38 (28/2.70)	2.05 (1.10, 3.83)	2,763	10.39 (28/2.69)	1.65 (0.99, 2.72)

Supplemental table S4: Continued.

Variable	Univariable analysis			Multivariable analysis		
	N	Crude IR (No./1000 person-years)	Unadjusted IRR (95%CI)	N	Crude IR (No./1000 person-years)	Adjusted IRR (95%CI)
Urologic diseases or conditions						
No	81,980	5.61 (449/80.08)	1.00	81,923	5.61 (449/80.02)	1.00
Yes	11,821	7.55 (87/11.53)	1.40 (1.00, 1.97)	11,812	7.55 (87/11.52)	0.89 (0.65, 1.23)
Depression						
No	87,825	5.78 (496/85.82)	1.00	87,763	5.78 (496/85.76)	1.00
Yes	5,976	6.92 (40/5.78)	1.24 (0.78, 1.98)	5,972	6.92 (40/5.78)	0.77 (0.50, 1.19)
Fracture						
No	86,756	5.20 (441/84.78)	1.00	86,698	5.21 (441/84.72)	1.00
Yes	7,045	13.93 (95/6.82)	2.97 (2.04, 4.33)	7,037	13.94 (95/6.81)	1.54 (1.12, 2.12)
Prior severe hypoglycemia						
No	93,491	4.59 (419/91.31)	1.00	93,425	4.59 (419/91.25)	1.00
Yes	310	401.50 (117/0.29)	87.09 (35.75, 212.13)	310	401.50 (117/0.29)	38.93 (20.40, 74.28)
Glucose-lowering drugs						
Biguanide	6,936	0.88 (6/6.79)	1.00	6,936	0.88 (6/6.79)	1.00
DPP-4i	29,893	3.47 (101/29.12)	3.98 (1.70, 9.35)	29,893	3.47 (101/29.12)	1.51 (0.64, 3.57)
SGLT-2i	3,362	0.30 (1/3.28)	0.34 (0.04, 2.94)	3,362	0.30 (1/3.28)	0.32 (0.04, 2.70)
Glinide	504	24.37 (12/0.49)	27.27 (7.82, 95.17)	504	24.37 (12/0.49)	3.52 (0.80, 15.46)
SU	2,434	5.49 (13/2.37)	6.27 (2.20, 17.84)	2,434	5.49 (13/2.37)	4.08 (1.46, 11.38)
GLP-1RA, thiazolidine, α glucosidase inhibitor	4,183	3.42 (14/4.09)	3.98 (1.45, 10.94)	4,183	3.42 (14/4.09)	1.66 (0.59, 4.69)
Insulin ^a	1,865	52.47 (93/1.77)	68.62 (26.82, 175.59)	1,865	52.47 (93/1.77)	15.14 (6.09, 37.62)
SU combination ^b	5,976	5.99 (35/5.84)	7.05 (2.82, 17.62)	5,976	5.99 (35/5.84)	4.03 (1.61, 10.10)
Glinide combination ^c	1,055	28.19 (29/1.03)	32.51 (11.47, 92.13)	1,055	28.19 (29/1.03)	4.38 (1.46, 13.14)
BOT ^d	699	17.86 (12/0.67)	20.62 (6.29, 67.59)	699	17.86 (12/0.67)	6.93 (2.17, 22.16)
Basal insulin+GLP-1RA	66	0.00 (0/0.06)	—	0	—	—
Other types of insulin combination ^e	2,090	32.12 (65/2.02)	37.60 (14.73, 95.99)	2,090	32.12 (65/2.02)	18.61 (7.48, 46.30)
DPP-4i combination ^f	12,572	2.44 (30/12.32)	2.79 (1.12, 6.96)	12,572	2.44 (30/12.32)	1.86 (0.74, 4.63)
Other 2-drug combination ^g	1,910	1.61 (3/1.87)	1.83 (0.43, 7.85)	1,910	1.61 (3/1.87)	1.66 (0.39, 7.03)
3-or-more-drug combination	20,256	6.14 (122/19.86)	7.02 (2.99, 16.46)	20,256	6.14 (122/19.86)	4.63 (1.96, 10.93)
Prior treatment with glucose-lowering drugs						
Previously treated	72,085	6.91 (487/70.46)	1.00	72,023	6.92 (487/70.40)	1.00
Untreated	21,716	2.32 (49/21.15)	0.36 (0.27, 0.47)	21,712	2.32 (49/21.14)	1.12 (0.77, 1.63)
No. of drugs						
≤4 (no polypharmacy)	40,956	2.69 (108/40.10)	1.00	40,919	2.70 (108/40.06)	1.00
5–9 (polypharmacy)	40,749	5.65 (225/39.86)	2.13 (1.62, 2.80)	40,731	5.65 (225/39.84)	1.13 (0.83, 1.55)
≥10 (excessive polypharmacy)	12,096	17.43 (203/11.64)	6.94 (5.03, 9.57)	12,085	17.45 (203/11.63)	1.57 (1.07, 2.30)

Incidence rate was calculated as the number of occurrences of severe hypoglycemia/total follow-up period across all patients at risk for the endpoint.

a. Basal insulin, other types of insulin

b. SU+biguanide, DPP-4i, SGLT-2i, glinide, GLP-1RA, thiazolidine, α glucosidase inhibitor

c. Glinide+biguanide, DPP-4i, SGLT-2i, GLP-1RA, thiazolidine, α glucosidase inhibitor

d. Basal insulin+biguanide, DPP-4i, glinide, SU, thiazolidine, α glucosidase inhibitor

e. Other types of insulin+biguanide, DPP-4i, SGLT-2i, glinide, SU, GLP-1RA, thiazolidine, α glucosidase inhibitor, basal insulin

f. DPP-4i+biguanide, SGLT-2i, GLP-1RA, thiazolidine, α glucosidase inhibitor

g. 2 drugs including biguanide, SGLT-2i, GLP-1RA, thiazolidine, α glucosidase inhibitor

BOT, basal insulin-supported oral therapy; CBVD, cerebrovascular disease; CHF, congestive heart failure; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease;

DPP-4i, dipeptidyl peptidase-4 inhibitor; ESRD, end-stage renal disease; GLP-1RA, glucagon-like peptide-1 receptor agonist; IR, incidence rate; IRR, incidence rate ratio; SGLT-2i, sodium glucose cotransporter-2 inhibitor;

SU, sulfonylurea.

Supplemental table S5 : Status of glycemic control (sub-cohort analysis)

	<i>N</i> (% ^a)	HbA1c (%)	Patients who achieved HbA1c <7.0%, <i>n</i> (% ^b)
Overall	26,746	6.87±0.95	17,029 (63.7)
Sex			
Male	17,717 (66.2)	6.91±0.98	10,946 (61.8)
Female	9,029 (33.8)	6.80±0.90	6,083 (67.4)
Age category (years)			
18–44	1,233 (4.6)	7.20±1.37	628 (50.9)
45–64	9,720 (36.3)	7.00±1.05	5,630 (57.9)
65–74	10,742 (40.2)	6.82±0.85	7,094 (66.0)
≥75	5,051 (18.9)	6.65±0.79	3,677 (72.8)
Type of insurance			
SHI	9,608 (35.9)	7.02±1.08	5,474 (57.0)
NHI	11,982 (44.8)	6.84±0.89	7,797 (65.1)
LSEHS	5,156 (19.3)	6.65±0.79	3,758 (72.9)
No. of beds in medical institution ^c			
Not prescribed	3,781 (14.1)	6.88±1.13	2,459 (65.0)
≤19	22,120 (82.7)	6.87±0.92	14,038 (63.5)
20–99	280 (1.0)	6.78±0.87	185 (66.1)
100–199	196 (0.7)	6.97±1.12	114 (58.2)
≥200	392 (1.5)	6.84±1.00	247 (63.0)
Comorbidities			
Dementia	459 (1.7)	6.66±0.83	327 (71.2)
ESRD, dialysis	46 (0.2)	6.39±1.01	36 (78.3)
CKD, excluding dialysis	5,587 (20.9)	6.87±0.95	3,533 (63.2)
Myocardial infarction	807 (3.0)	6.80±0.92	544 (67.4)
CHF	3,189 (11.9)	6.71±0.91	2,257 (70.8)
CBVD	4,427 (16.6)	6.76±0.88	3,020 (68.2)
COPD	2,861 (10.7)	6.80±0.93	1,893 (66.2)
Malignancy, excluding malignant skin neoplasm	2,148 (8.0)	6.74±0.87	1,482 (69.0)
Cirrhosis	213 (0.8)	6.84±1.15	137 (64.3)
Diabetic retinopathy	5,552 (20.8)	7.05±0.99	3,047 (54.9)
Diabetic neuropathy	1,108 (4.1)	7.12±1.04	592 (53.4)
Hypertension	17,622 (65.9)	6.82±0.92	11,579 (65.7)
Arthritis	644 (2.4)	6.66±0.87	465 (72.2)
Urologic diseases or conditions	3,122 (11.7)	6.74±0.86	2,149 (68.8)
Depression	1,322 (4.9)	6.80±1.10	902 (68.2)
Fracture	1,416 (5.3)	6.77±0.91	944 (66.7)
Multimorbidity			
No	3,864 (14.4)	6.97±1.05	2,302 (59.6)
Yes	22,882 (85.6)	6.85±0.94	14,727 (64.4)
No. of comorbidities			
1	3,864 (14.4)	6.97±1.05	2,302 (59.6)
2	8,509 (31.8)	6.89±0.95	5,376 (63.2)
3	6,796 (25.4)	6.86±0.94	4,305 (63.3)
4	4,064 (15.2)	6.80±0.90	2,698 (66.4)
5	2,062 (7.7)	6.79±0.93	1,393 (67.6)
6	944 (3.5)	6.80±0.92	625 (66.2)
7	340 (1.3)	6.78±0.88	216 (63.5)
≥8	167 (0.6)	6.84±1.22	114 (68.3)
No. of occurrences of severe hypoglycemia			
0	26,709 (99.9)	6.87±0.95	17,006 (63.7)
1	33 (0.1)	7.11±1.26	19 (57.6)
≥2	4 (0.0)	6.38±0.51	4 (100.0)

Supplemental table S5 : Continued.

	N (% ^a)	HbA1c (%)	Patients who achieved HbA1c <7.0%, n (% ^b)
Glucose-lowering drugs			
None	3,781 (14.1)	6.88±1.13	2,459 (65.0)
Biguanide	1,858 (6.9)	6.67±0.70	1,353 (72.8)
DPP-4i	6,541 (24.5)	6.59±0.71	5,013 (76.6)
SGLT-2i	886 (3.3)	6.64±0.76	664 (74.9)
Glinide	120 (0.4)	6.63±0.74	89 (74.2)
SU	482 (1.8)	6.87±0.94	299 (62.0)
GLP-1RA	59 (0.2)	6.92±1.18	34 (57.6)
Thiazolidine	365 (1.4)	6.36±0.62	313 (85.8)
α glucosidase inhibitor	641 (2.4)	6.39±0.63	540 (84.2)
Basal insulin	96 (0.4)	7.88±1.64	28 (29.2)
Other types of insulin	253 (0.9)	7.41±1.44	111 (43.9)
SU+biguanide	209 (0.8)	7.21±0.91	102 (48.8)
SU+DPP-4i	832 (3.1)	7.16±1.01	396 (47.6)
SU+SGLT-2i	39 (0.1)	7.55±1.01	11 (28.2)
SU+other glucose-lowering drugs ^d	174 (0.7)	6.82±0.85	109 (62.6)
BOT ^e	129 (0.5)	7.46±1.62	60 (46.5)
Basal insulin+GLP-1RA	25 (0.1)	7.56±1.64	8 (32.0)
Biguanide+DPP-4i	2,346 (8.8)	6.87±0.86	1,515 (64.6)
Biguanide+SGLT-2i	241 (0.9)	6.95±0.90	146 (60.6)
Biguanide+other glucose-lowering drugs ^d	328 (1.2)	6.67±0.71	230 (70.1)
DPP-4i+SGLT-2i	451 (1.7)	6.96±0.79	250 (55.4)
DPP-4i+other glucose-lowering drugs ^d	931 (3.5)	6.73±0.81	655 (70.4)
SGLT-2i+other glucose-lowering drugs ^d	57 (0.2)	6.96±1.14	34 (59.6)
Other types of insulin combination ^f	417 (1.6)	7.48±1.28	166 (39.8)
Other glucose-lowering drug ^d combination	123 (0.5)	6.78±0.94	81 (65.9)
3-or-more-drug combination	5,362 (20.0)	7.26±1.01	2,363 (44.1)
Class of glucose-lowering drugs			
None	3,781 (14.1)	6.88±1.13	2,459 (65.0)
Monotherapy	11,301 (42.3)	6.63±0.78	8,444 (74.7)
2-drug combination therapy	6,302 (23.6)	6.96±0.96	3,763 (59.7)
3-or-more-drug combination therapy	5,362 (20.0)	7.26±1.01	2,363 (44.1)
No. of drugs			
≤4 (no polypharmacy)	15,141 (56.6)	6.89±0.97	9,591 (63.3)
5–9 (polypharmacy)	9,883 (37.0)	6.86±0.93	6,293 (63.7)
≥10 (excessive polypharmacy)	1,722 (6.4)	6.78±0.97	1,145 (66.5)

Data for HbA1c presented as mean±SD.

a. Percentage indicates proportion of all patients (overall).

b. Percentage indicates n/N for each category.

c. Some overlap in counting is acceptable.

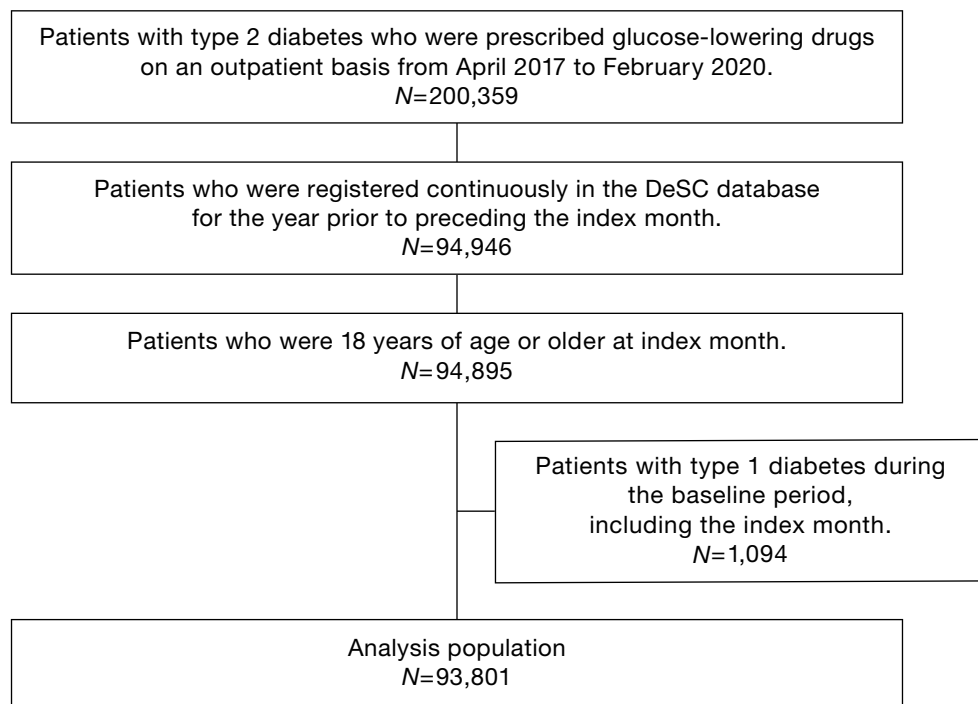
d. Glinide, GLP-1RA, thiazolidine, α glucosidase inhibitor

e. Basal insulin+biguanide, DPP-4i, SGLT-2i, glinide, SU, thiazolidine, α glucosidase inhibitor

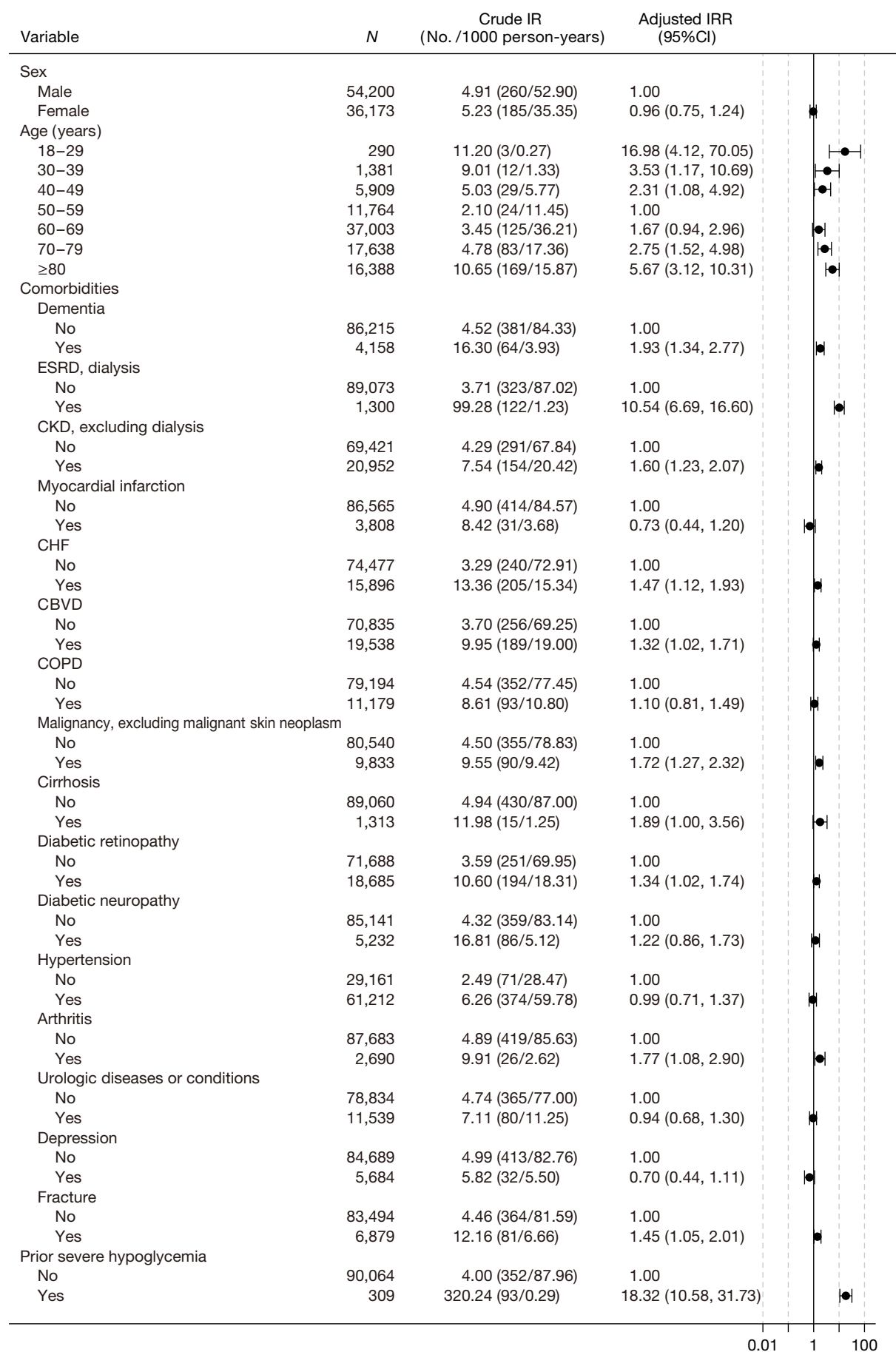
f. Other types of insulin+biguanide, DPP-4i, SGLT-2i, glinide, SU, GLP-1RA, thiazolidine, α glucosidase inhibitor, basal insulin

BOT, basal insulin supported oral therapy; CBVD, cerebrovascular disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DPP-4i, dipeptidyl peptidase-4 inhibitor; ESRD, end-stage renal disease; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, hemoglobin A1c; LSEHS, latter-stage elderly health care system; NHI, national health insurance; SHI, society-managed employment-based health insurance association; SGLT-2i, sodium glucose cotransporter-2 inhibitor; SD, standard deviation; SU, sulfonylurea.

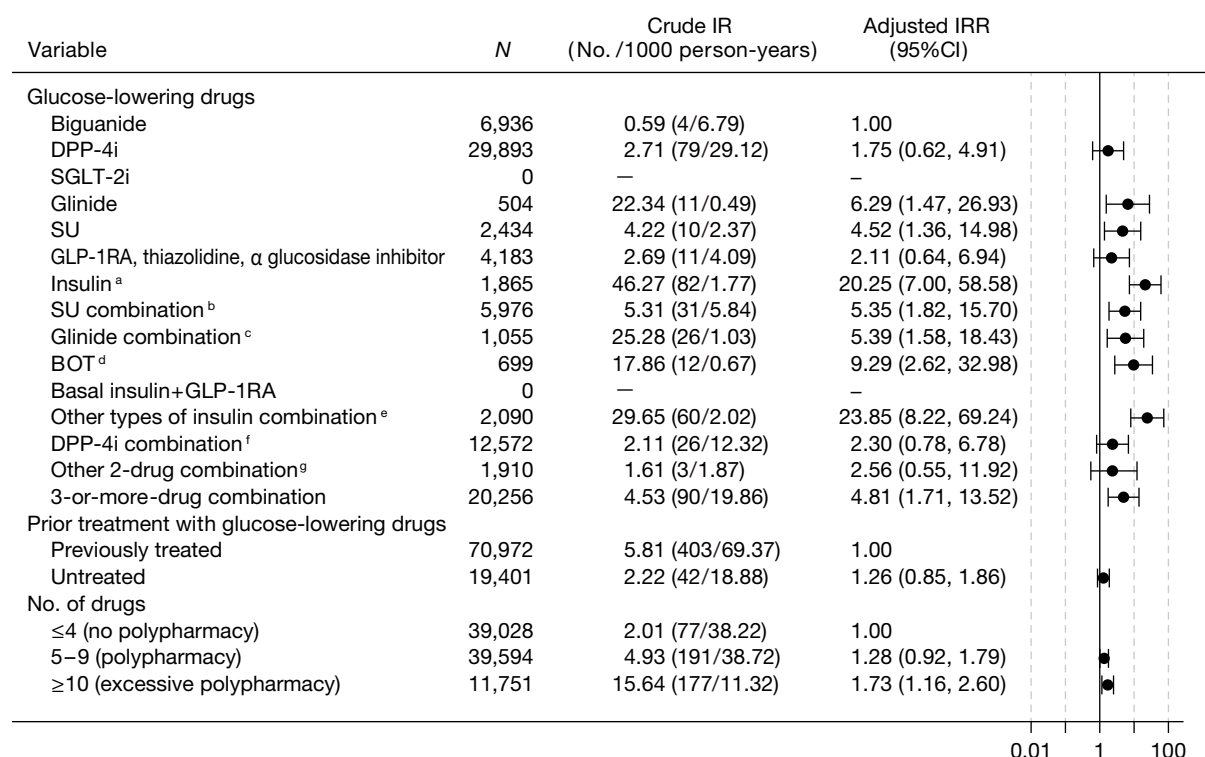
Supplemental figure S1: Patient disposition



Supplemental figure S2 : Factors affecting the incidence rate of severe hypoglycemia (sensitivity analysis)



Supplemental figure S2 : Continued.



The explanatory variables that were included in the negative binomial regression model were age, sex, comorbidity, glucose-lowering drugs, polypharmacy, prior severe hypoglycemia, and prior glucose-lowering therapy at baseline, with log-transformed follow-up time as an offset. The IRR was calculated for each comorbidity, using the absence of that comorbidity as the reference value (not shown here). If no hypoglycemic episodes were recorded, data for that category were not analysed. The forest plot shows the point estimate and 95% CI for the IRR in multivariable analysis.

Incidence rate was calculated as the number of occurrences of severe hypoglycemia/total follow-up period across all patients at risk for the endpoint.

a. Basal insulin, other types of insulin

b. SU+biguanide, DPP-4i, SGLT-2i, glinide, GLP-1RA, thiazolidine, α glucosidase inhibitor

c. Glinide+biguanide, DPP-4i, SGLT-2i, GLP-1RA, thiazolidine, α glucosidase inhibitor

d. Basal insulin+biguanide, DPP-4i, SGLT-2i, glinide, SU, thiazolidine, α glucosidase inhibitor

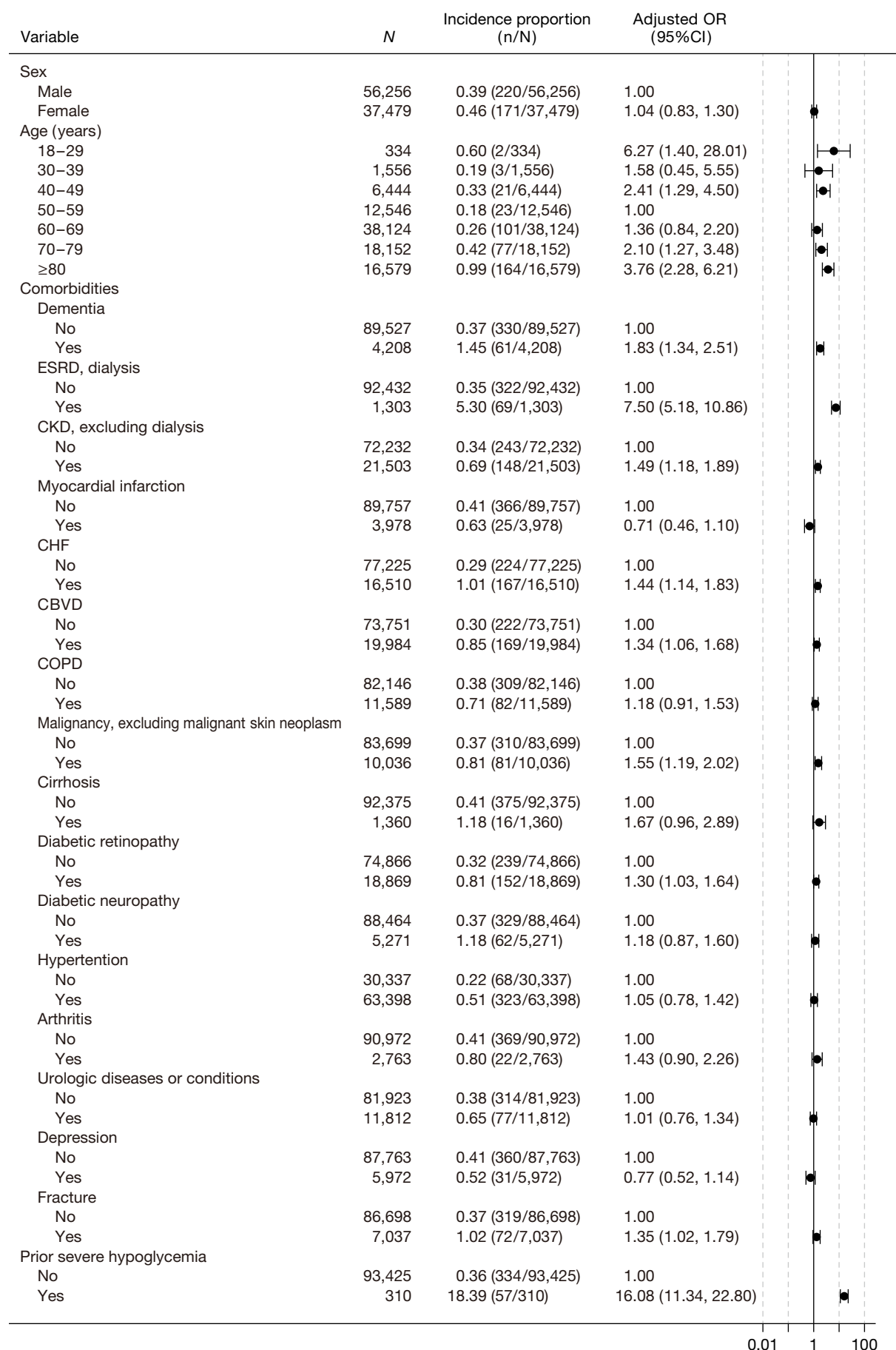
e. Other types of insulin+biguanide, DPP-4i, SGLT-2i, glinide, SU, GLP-1RA, thiazolidine, α glucosidase inhibitor, basal insulin

f. DPP-4i+biguanide, SGLT-2i, GLP-1RA, thiazolidine, α glucosidase inhibitor

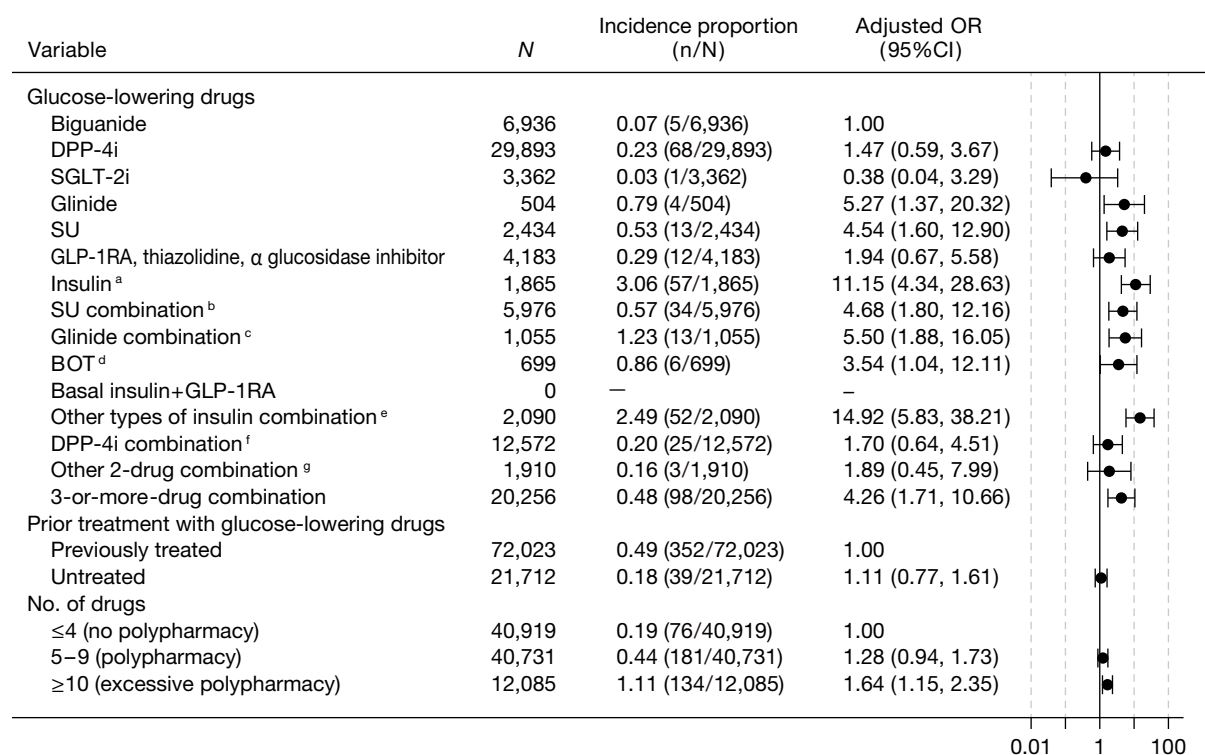
g. 2 drugs including biguanide, SGLT-2i, GLP-1RA, thiazolidine, α glucosidase inhibitor

BOT, basal insulin-supported oral therapy; CBVD, cerebrovascular disease; CI, confidence interval; CKD, chronic kidney disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DPP-4i, dipeptidyl peptidase-4 inhibitor; ESRD, end-stage renal disease; GLP-1RA, glucagon-like peptide-1 receptor agonist; IR, incidence rate; IRR, incidence rate ratio; SGLT-2i, sodium glucose cotransporter-2 inhibitor; SU, sulfonylurea.

**Supplemental figure S3: Factors affecting the occurrence of severe hypoglycemia
(multivariable logistic analysis)**



Supplemental figure S3: Continued.



The explanatory variables that were included in the logistic regression model were age, sex, comorbidity, glucose-lowering drugs, polypharmacy, prior severe hypoglycemia, and prior glucose-lowering therapy during the baseline period. The OR was calculated for each comorbidity, using the absence of that comorbidity as the reference value (not shown here). If no hypoglycemic episodes were recorded, data for that category were not analysed. The forest plot shows the point estimate and 95% CI for the OR in multivariable analysis.

a. Basal insulin, other types of insulin

b. SU+biguanide, DPP-4i, SGLT-2i, glinide, GLP-1RA, thiazolidine, α glucosidase inhibitor

c. Glinide+biguanide, DPP-4i, SGLT-2i, GLP-1RA, thiazolidine, α glucosidase inhibitor

d. Basal insulin+biguanide, DPP-4i, SGLT-2i, glinide, SU, thiazolidine, α glucosidase inhibitor

e. Other types of insulin+biguanide, DPP-4i, SGLT-2i, glinide, SU, GLP-1RA, thiazolidine, α glucosidase inhibitor, basal insulin

f. DPP-4i+biguanide, SGLT-2i, GLP-1RA, thiazolidine, α glucosidase inhibitor

g. 2 drugs including biguanide, SGLT-2i, GLP-1RA, thiazolidine, α glucosidase inhibitor

BOT, basal insulin-supported oral therapy; CBVD, cerebrovascular disease; CI, confidence interval; CKD, chronic kidney disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DPP-4i, dipeptidyl peptidase-4 inhibitor; ESRD, end-stage renal disease; GLP-1RA, glucagon-like peptide-1 receptor agonist; OR, odds ratio; SGLT-2i, sodium glucose cotransporter-2 inhibitor; SU, sulfonylurea.