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Risk of non-hypoglycemic agents for hypoglycemia-related hospitalization in patients with type 2 diabetes: a large-scale medical receipt database analysis

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ABSTRACT

Introduction Hypoglycemia is listed as an adverse effect in the package inserts of not only hypoglycemic agents but also many other drugs. We aimed to clarify real-world factors related to an increased risk of hypoglycemia-related hospitalization (HRH) in Japanese patients with type 2 diabetes (T2D) on non-hypoglycemic agents that have been associated with hypoglycemia.

Research design and methods This cross-sectional study was performed using data from the Medical Data Vision administrative claims database. We identified patients with T2D who were enrolled in the database between April 2014 and October 2019. Logistic regression analyses were performed to identify clinical factors associated with HRH due to non-hypoglycemic agents.

Results Among 703 745 patients with T2D, 10 376 patients (1.47%) experienced HRH. The use of 332 non-hypoglycemic agents was associated with hypoglycemia. Multivariate analysis was performed to calculate OR for HRH. Seventy-five drugs had an OR greater than 1, and the values were significant. The OR was the highest for diazoxide (OR 15.5, 95% CI 4.87 to 49.3). The OR was higher than 2.0 for methylphenidate (OR 5.15, 95% CI 1.53 to 17.3), disulfiram (OR 4.21, 95% CI 2.05 to 8.62) and hydrocortisone (OR 2.89, 95% CI 1.11 to 7.51).

Conclusion This large retrospective analysis revealed that the risk of HRH from some non-hypoglycemic agents in patients with T2D may be increased. The results of this study are expected to support treatment planning by physicians and healthcare professionals involved in diabetes care.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The mechanisms of action of hypoglycemic agents differ, depending on the drug group, and each group has characteristic side effects. Nevertheless, the most notable side effect common to all hypoglycemic agents is hypoglycemia.

⇒ Hypoglycemia is listed as an adverse effect in the package inserts of not only hypoglycemic agents but also many other drugs.

WHAT THIS STUDY ADDS

⇒ In this real-world retrospective analysis, we were able to clarify factors related to an increased risk of hypoglycemia-related hospitalization (HRH) in Japanese patients with type 2 diabetes on non-hypoglycemic agents that have been associated with hypoglycemia.

⇒ In this study, we elucidated the OR of HRH was particularly elevated with diazoxide, disulfiram and hydrocortisone use.

⇒ We were able to clarify other factors that were associated with a higher risk of hypoglycemia, such as a body mass index of <25 kg/m^2.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ By considering the comorbidities and various concomitant drugs of individual patients and clarifying the risk of HRH under various conditions, the risk of hypoglycemia may be minimized.

INTRODUCTION

In Japan, the goal of type 2 diabetes (T2D) treatment is to achieve good glycemic control. To do this, clinicians are free to use two injectable hypoglycemic drugs and seven oral hypoglycemic drugs. The mechanisms of action of hypoglycemic agents differ, depending on the drug group, and each group has characteristic side effects. Nevertheless, the most notable side effect common to all hypoglycemic agents is hypoglycemia.[1] Therefore, utmost attention should be paid to it since it is associated with decreased quality of life,[2] decreased work efficiency,[3] and increased risk of falls and car accidents.[4] Furthermore, hypoglycemia due to T2D drug therapies has been reported to increase the risk of cardiovascular events,[5 6] dementia,[7 8] and death.[9 10] Hypoglycemia is listed as an adverse effect in the package inserts of not only hypoglycemic agents but also many other drugs. It is speculated that hypoglycemia caused by non-hypoglycemic agents is more likely to be severe in patients with T2D taking hypoglycemic agents than in those not taking hypoglycemic agents. It is considered that patients taking hypoglycemic medications

pay attention to severe hypoglycemia caused by hypoglycemic medications but do not pay enough attention to hypoglycemia caused by non-hypoglycemic medications. By investigating the relationship between concomitantly used drugs other than hypoglycemic agents and hypoglycemia in detail, hypoglycemia severe enough to require hospitalization could be prevented in patients with T2D. Therefore, in this study, we aimed to clarify real-world factors related to an increased risk of hypoglycemia-related hospitalization (HRH) in Japanese patients with T2D on non-hypoglycemic agents that have been reported to be associated with hypoglycemia.

METHODS

This real-world, cross-sectional study was performed using data from the Medical Data Vision (MDV) administrative claims database (MDV Co., Tokyo, Japan). The aforementioned database is a nationwide hospital-based claims database covering almost 31 million cumulative patients since April 2008, who, as of October 2019, had been treated as inpatients or outpatients at approximately 360 hospitals in Japan (21% of the total number of hospitals) that participated in the diagnosis procedure combination/per-diem payment system. Approximately 3 million (~10%) of these patients were diagnosed with diabetes mellitus (DM). The MDV database contains anonymized information about patient characteristics, diagnoses, medical expenses, medical procedures, and drug prescriptions. All patient data were encrypted before entry into the database. Data on administrative claims made from April 1, 2014, to October 31, 2019, were extracted. Patients with T2D who did not develop HRH were observed until the end of the study period, and if a patient developed hypoglycemia at a particular time point during the study period, observation was terminated at that time point for the said patient.

Study population

Information was obtained for 3 129 105 patients registered in the MDV database from April 1, 2008, to October 31, 2019. In addition, data for patients diagnosed with DM (International Classification of Diseases, 10th Edition (ICD-10) code: E10-E14) were extracted. The following patients were excluded (figure 1): (1) patients not using hypoglycemic agents (n=1 460 086); (2) patients without BMI data (n=860 035); (3) patients under the age of 20 years (n=1838); and (4) patients diagnosed with type 1 diabetes (T1D, ICD-10 code: E10), both T1D and T2D and with other types of DM, except T1D and T2D (n=103 810). As a result, 703 745 patients with T2D were eligible for inclusion.

Identification of HRH

HRH events were identified based on previous definitions.[11 12] Hospitalizations for hypoglycemia in the MDV database were identified using the following ICD-9 codes: 251.0 (hypoglycemic coma), 251.1 (other specified hypoglycemia), and 251.2 (hypoglycemia, unspecified).

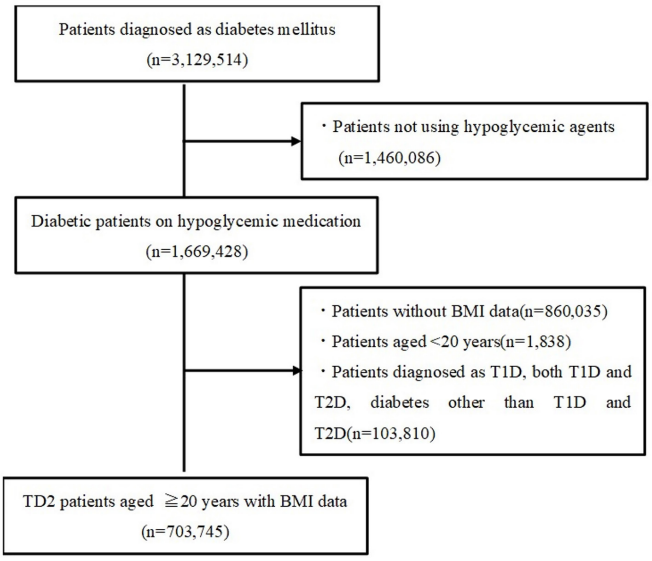

Figure 1 Characteristics of the patients. BMI, body mass index; T1D, type 1 diabetes; T2D, type 2 diabetes.

Additionally, the following ICD-10 codes were used: E08.641, E11.641, E11.649, E13.64, E13.641, E13.649, E16.0, E16.1, E15, and E16.2. Patients who did not receive a 50% glucose injection on the day of admission were excluded. HRH was defined as hospitalization due to hypoglycemia that met the aforementioned conditions.

Patient characteristics

Age, sex, and body mass index (BMI) were included as baseline characteristics and identified using the data originally provided in the billing record during the period covered. Obesity was defined as a BMI of 25 kg/m^2 or higher according to Japanese guidelines.[13]

Non-hypoglycemic agents that have been reported to be associated with hypoglycemia

Details of the non-hypoglycemic agents that have been reported to be associated with hypoglycemia are shown in online supplemental table 1. In Japan, drug manufacturers and pharmaceutical personnel are required by law to report cases suspected to be due to side effects when they become aware of them. The reported cases are published by the Pharmaceuticals and Medical Devices Agency (PMDA) in the line list and CSV file formats. Drugs reported to be associated with the onset of hypoglycemia were extracted from the data published by the PMDA and used as the target drugs.

Statistical analysis

Patient data following a normal distribution (age, BMI, hemoglobin A1C (HbA1c), and estimated glomerular filtration rate (eGFR)) are expressed as mean±SD values. Continuous variables were analyzed using a one-tailed, unpaired t-test. Categorical variables were analyzed using the χ^2 test and are expressed as absolute numbers and/or percentages. ORs for the risk of HRH were analyzed using univariate analysis. The explanatory variables used

Table 1 Baseline clinical characteristics of patients with T2D

	Total (N=703 745)	HRH (+) (N=10 376)	HRH (–) (N=693 369)	P value
Sex				
Male	434 569 (61.8)	6274 (60.5)	428 295 (61.8)	0.007
Female	269 176 (38.2)	4102 (39.5)	265 074 (38.2)	
Age (years)	70.4±12.3	71.8±11.5	70.4±12.2	<0.001
20–64	190 603 (27.1)	2350 (22.6)	188 253 (27.2)	<0.001
65–74	227 115 (32.3)	3280 (31.6)	223 835 (32.3)	
≥75	286 027 (40.6)	4746 (45.7)	281 281 (40.6)	
BMI (kg/m^2)	24.1±4.3	22.7±4.3	24.1±4.3	<0.001
≥25	256 330 (36.4)	2516 (24.2)	253 814 (36,6)	<0.001
<25	447 415 (63.6)	7860 (75.8)	439 555 (63.4)	
Hypoglycemic agents				
Biguanides	203 923 (29.0)	2616 (25.2)	201 307 (29.0)	<0.001
DPP-4 inhibitors	469 393 (66.7)	7173 (69.1)	462 220 (66.7)	<0.001
Glinides	81 736 (11.6)	2039 (19.7)	79 697 (11.5)	<0.001
GLP-1 RA	32 171 (4.6)	831 (8.0)	31 340 (4.5)	<0.001
Insulin	445 129 (63.3)	8910 (85.9)	436 219 (62.9)	<0.001
SGLT2 inhibitors	72 315 (10.3)	726 (7.0)	71 589 (10.3)	<0.001
Sulfonylureas	192 847 (27.4)	4207 (40.5)	188 640 (27.2)	<0.001
Thiazolidines	65 737 (9.3)	1384 (13.3)	64 353 (9.3)	<0.001
α-GI	158 055 (22.5)	3738 (36.0)	154 317 (22.3)	<0.001

P values were calculated for differences between patients with and without hypoglycemic events.
BMI, body mass index; DPP-4, dipeptidyl peptidase-4; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HRH (+), patients with HRH events; HRH, hypoglycemia-related hospitalization; HRH (–), patients without HRH events; SGLT2, sodium-glucose co-transporter 2; T2D, type 2 diabetes; α-GI, alpha-glucosidase inhibitor.

in the univariate analysis were administration of antidiabetic agents (yes/no), non-hypoglycemic agents that have been reported to be associated with hypoglycemia (yes/no), sex, age (20–64, 65–74, and ≥75 years), and BMI (cut-off value: 25 kg/m^2). Multivariate analysis was performed using the explanatory variables for which the p value was <0.2 in the univariate analysis. All statistical analyses were performed using IBM SPSS Statistics for Windows V.25.0 (IBM Corp., Armonk, NY).

RESULTS

During the study period, 703 745 patients with T2D were included. Table 1 shows the characteristics of the patients with T2D in this study. The mean patient age and BMI were 70.4±12.3 years and 24.1±4.3 kg/m^2, respectively. HRH developed in 10 376 patients (1.47%). Compared with the patients without HRH, those with T2D having HRH included more men, were older, and had lower BMIs.

Online supplemental table 1 shows the use of 331 of non-hypoglycemic agents reportedly associated with HRH. The frequency of use of 43 drugs was significantly different between patients with T2D who experienced HRH and those who did not experience HRH (online supplemental table 2).

Next, the risk of HRH was examined by calculating OR using patient background, hypoglycemic agents, and non-hypoglycemic agents, which have been reported to

Table 2 Logistic regression analysis for predictors of hypoglycemia-related hospitalization in T2D

	OR	95% CI	P value
Sex			
Male	Reference	–	0.012
Female	1.05	1.01 to 1.10	
Age (years)			
20–64	Reference	–	
65–74	1.03	0.97 to 1.08	0.331
≥75	1.10	1.04 to 1.16	<0.001
BMI (kg/m^2)			
≥25	Reference	–	<0.001
<25	1.61	1.54 to 1.69	

BMI, body mass index; T2D, type 2 diabetes.

be associated with hypoglycemia as an explanatory variable (table 2). Compared with an age of <65 years, an age of ≥75 years was associated with an increased OR for HRH (OR 1.1, 95% CI 1.04 to 1.16). The value was significant for BMI of <25 kg/m^2 (OR 1.61, 95% CI 1.54 to 1.69) with BMI of ≥25 kg/m^2 serving as the reference. Online supplemental table 3 shows the ORs for the individual components of the hypoglycemic agents. The ORs for insulin and Sulfonilureas (SU) agents were high, whereas the ORs for all SGLT2 inhibitors were less than 1.

Online supplemental table 4 shows the results of the multivariate analysis of non-hypoglycemic agents that have been reported to be associated with hypoglycemia. Seventy-five drugs had an OR greater than 1 and the values were significant. The OR was the highest for diazoxide (OR 15.5, 95% CI 4.87 to 49.3). The OR was higher than 2.0 for methylphenidate (OR 5.15, 95% CI 1.53 to 17.3), disulfiram (OR 4.21, 95% CI 2.05 to 8.62), and hydrocortisone (OR 2.89, 95% CI 1.11 to 7.51).

DISCUSSION

Patients with T2D develop multimorbidity because of persistent hyperglycemia, and thus, they are prescribed more drugs compared with those prescribed to patients with other disorders.[14] In this study, we analyzed non-hypoglycemic agents that have been reported to be associated with hypoglycemia. The strength of this study is that we were able to clarify the risk of developing HRH in settings that better reflect actual settings in which drug therapy is used for the management of T2D compared with those in previous studies. In our study, approximately 1.5% of patients with T2D showed HRH. Although the definitions of hypoglycemia severity are not identical, the incidence of HRH in this study was slightly higher than that reported in multiple intervention studies.[15–17] The reason for this is that the observation period was longer than in these studies, and the age of the patients with T2D in this study was approximately 70 years. In our study, a higher proportion of elderly people and an insulin usage rate as high as approximately 70% seem to affect the incidence of HRH. Patients associated with an increased risk of developing HRH in this study were women aged ≥75 years or with a BMI of <25 kg/m^2. The most frequently reported association with the risk of developing hypoglycemia was in the elderly.[18–20] Elderly patients with T2D have many comorbidities and are at an increased risk of polypharmacy. In the ACCORD trials,[8] the lower the BMI, the higher the risk of developing severe hypoglycemia, and a survey report on severe hypoglycemia conducted in Japan[21] showed similar results. Patients with a low BMI are presumed to have endogenously impaired insulin secretion or to be elderly patients with frailty or sarcopenia-related weight loss. In a cohort study of the risk of developing severe hypoglycemia among patients with T2D in Japan, there was no difference in the risk of developing severe hypoglycemia between men and women.[22] In this study, the risk slightly increased to 1.05 for female patients, with male patients serving as the reference. Ikeda *et al* reported that the OR for severe hypoglycemia increased among women in a study limited to elderly patients with T2D,[23] and it is necessary to investigate the details in the future.

We also examined the non-hypoglycemic agents that have been reported to be associated with hypoglycemia. The ORs for the onset of HRH were significant in the cases of 75 types of drugs, with ORs being higher than 2.0 for diazoxide, methylphenidate, disulfiram, and hydrocortisone. The OR for diazoxide was the highest (23.13). Diazoxide is used to treat low blood sugar levels due to several specific causes.[24] In other words, it is considered to have the highest OR because it is actively administered to patients with HRH. The next highest OR was that for methylphenidate. Loss of appetite is a well-known side effect of methylphenidate.[25 26] Skipping food or reducing food intake is a major risk factor for the development of severe hypoglycemia.[27] Since the patients with T2D targeted in this study were on at least one hypoglycemic agent, it is thought that the OR was high because the appetite-suppressing effect of methylphenidate caused HRH. Disulfiram is an irreversible aldehyde dehydrogenase inhibitor approved for the treatment of chronic alcoholism.[28] It has been confirmed to have a strong anti-obesity effect in in vivo studies[29] and a hypoglycemic effect[30 31] by inhibiting fructose 1,6-bisphosphatase activity. In addition, it is speculated that patients with T2D on disulfiram may develop hepatic dysfunction due to habitual alcohol intake. Owing to a combination of these factors, disulfiram is thought to have increased the OR for the onset of HRH. Hydrocortisone is used to treat adrenocortical insufficiency. Since hypoglycemia is one of the typical symptoms of adrenocortical insufficiency, it is considered that the OR for HRH increased in this study. Other frequently reported drug-induced hypoglycemia include β-blockers, ACE inhibitors/angiotensin II receptor blockers (ARBs), and fluoroquinolone antibiotics.[32] In this study, ACE inhibitors (imidapril and enalapril) and ARBs (valsartan, irbesartan, telmisartan, olmesartan, losartan, and candesartan) were associated with an increased risk of developing HRH. ACE inhibitors and ARBs have been reported to improve insulin resistance by antagonizing the AT_1 receptor and activating the peroxisome proliferator-activated receptor-γ).[33 34] These actions improve insulin resistance and increase the risk of hypoglycemia. On the other hand, in T2D, the benefits of administering ACE inhibitors/ARBs, such as prevention of diabetic nephropathy progression, are very large. Since the increase in OR is not large, the risks and benefits should be considered while administering these agents. Among β-blockers, carteolol was associated with an increased risk of developing hypoglycemia (OR 1.61, 95% CI 1.37 to 1.88). Since insulin secretion from pancreatic β-cells is associated with autonomic nerves, β-blockers have been reported to increase the risk of developing hypoglycemia.[35] Furthermore, among β-blockers, β-1 selective blockers have been reported to increase the risk

of developing severe hypoglycemia[36]; therefore, selection of drugs that specifically target particular receptors is considered important. Fluoroquinolone antibiotics are thought to promote insulin secretion and induce hypoglycemia.[37] Gatifloxacin was withdrawn from the market due to concerns regarding severe glucose disturbances. Aspinall *et al*[38] reported that levofloxacin increased the risk of severe hypoglycemia. In addition to levofloxacin, prulifloxacin and moxifloxacin were associated with significant OR values for HRH in this study. Regarding the three fluoroquinolone antibiotics that showed significant values in this study, it is recommended that their package inserts specify HRH as a serious side effect and caution should be exercised while using these drugs. When these drugs are administered to patients with T2D having risk factors for developing HRH, fluctuations in blood glucose levels should be carefully monitored.

Limitations

This study has some limitations. The MDV database consists only of data from patients treated in hospitals where acute care is administered in Japan. Therefore, it is important to recognize that it does not represent data for all patients with T2D. However, the percentage of patients with T2D (11%) in the overall MDV database were fairly close to those used in the 2017 Japan Health and Nutrition Examination Survey (14%).[39] This suggests that the T2D data in the MDV dataset may closely represent the T2D scenario in Japan as a whole. In addition, information about specific confounders of hypoglycemia (eg, HbA1c and eGFR) was available only for a limited number of patients in the MDV database. For example, cinacalcet and furosemide are frequently used drugs for patients with considerably reduced renal function. Although the ORs for these drugs were not very high in this study, they were significant, suggesting that the reduced renal function may influence risk of HRH. In addition, there may also be unknown factors that increase the risk of HRH. This was particularly influential in the analysis of drugs that have been reported to cause hypoglycemia. For drugs with a high OR, such as disulfiram, it is necessary to focus on individual drugs and to eliminate the effects of comorbidities. It is also possible that confounding factors that could not be investigated in this study may have influenced factors that showed a slight increase in OR, such as gender. One of the features of the MDV Receipt Database is that a disease title may be assigned for the purpose of T2D testing. In this study, we were unable to determine whether T2D was diagnosed and not treated with hypoglycemic drugs or whether the disease was assigned a disease title for the purpose of testing. Therefore, we had to exclude patients with T2D who were not using hypoglycemic drugs from the study. In this study, the ORs for diazoxide and hydrocortisone were high. These drugs may be used to treat hypoglycemia for a variety of reasons, including insulinoma. As this study involved patients with T2D who were receiving hypoglycemic medications, it is unlikely that patients with insulinoma were included. On the contrary, we cannot rule out the possibility that patients with underlying blood glucose-lowering diseases, such as insulinoma, were not completely excluded, which may have influenced the results. The patients with T2D who were hospitalized for hypoglycemia may have been patients with conditions that make them susceptible to the hypoglycemic effects of non-hypoglycemic agents, such as having various comorbidities. As we were not able to collect detailed laboratory values or information on complications in this study, further details should be considered. Finally, this study did not consider the time between drug administration and the onset of HRH. To develop a plan for the prevention of HRH, it is important to understand the period from the administration of the drug to the onset of HRH. In this study, we focused on drugs that are strongly associated with the development of HRH, and we would like to perform further investigations using an analysis method that includes the passage of time.

CONCLUSION

This large retrospective analysis revealed that the risk of HRH from some non-hypoglycemic agents in patients with T2D may be increased. Early identification of risk and consideration of a personalized treatment plan are essential to minimize the development of HRH. The results of this study highlight the need for continued intervention strategies by physicians and healthcare professionals involved in diabetes treatment and support treatment planning.

Contributors TH and MO conceptualized the study, performed the literature search and statistical analysis, and analyzed the data. TH, MO and TY analyzed the results. TH wrote the manuscript and is responsible for the overall content as the guarantor.

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Competing interests TH received lecture fees from Kowa KK.

Patient consent for publication Not applicable.

Ethics approval The ethics board of Kitasato University admitted that the research protocol for this study does not require ethics approval because all available data are completely anonymous with no personal information, which is characteristic ofDiagnosis Procedure Combination(DPC)-based clinical databases (control number B19-285, dated January 31, 2020). All patient data were anonymized and contained no personal data; thus, informed consent was not required. This study was conducted in accordance with the Declaration of Helsinki and the ethical guidelines for medical and health research involving human subjects.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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Supplementary Table 1. List of non-hypoglycemic agents reportedly associated with hypoglycemia.

Abemaciclib	Enalapril	Ombitasvir/ Paritaprevir/Ritonavir
Abiraterone	Entacapone	Omeprazole
Acebutolol	Enteral nutrition	Oseltamivir
Acetazolamide	Enzalutamide	Oxycodone
Aciclovir	Erlotinib	Palbociclib
Acotiamide	Erythromycin	Paliperidone
Afatinib	Escitalopram	Paroxetine
Alendronate	Ethambutol	Pazopanib
Alfacalcidol	Etizolam	Pergolide
Allopurinol	Etodolac	Perospirone
Alprazolam	Etretinate	Phenytoin
Amantadine	Everolimus	Phytonadione
Amenamivir	Exemestane	Picosulfate
Amiodarone	Ezetimibe	Pilsicainide
Amitriptyline	Famotidine	Polycarbophil calcium
Amlodipine	Faropenem	Pramipexole
Amoxapine	febuxostat	Pranlukast
Amoxicillin	Fenofibrate	Precipitated calcium carbonate
Amoxicillin/ Potassium clavulanate	Fesoterodine	Prednisolone
Ampiroxicam	Flavoxate	Pregabalin
Antipyretic	Flecainide	Probenecid
Apixaban	Fluconazole	Promethazine
Aripiprazole	Flunitrazepam	Propafenone
Asenapine	fluvastatin	Propranolol
Aspirin	fluvoxamine	Propylthiouracil
Aspirin/ Lansoprazole combination	Forodesine	Prulifloxacin
Atenolol	Fosfomycin calcium	Pyrazinamide
Atorvastatin	Furosemide	Quetiapine
axitinib	Fursultiamine	Rabeprazole

Azathioprine	Gabapentin	Rabeprazole/ Amoxicillin/Clarithromycin
Azilsartan	Galantamine	Raloxifene
Azilsartan/ Amlodipine combination	Garenoxacin	Ramelteon
Azithromycin	Gatifloxacin	Regorafenib
Baloxavir marboxil	Gefitinib	Ribavirin
Bepridil	Glecaprevir/Pibrentasvir	Rifampicin
Beraprost	Guanfacine	Rifaximin
Betamethasone/d-chlorpheniramine	Haloperidol	Risperidone
Bexarotene	Hydrocortisone	Ritodrine
Bezafibrate	Hydroxycarbamide	Rivaroxaban
Bisoprolol	Hydroxychloroquine	Ropinirole
Blonanserin	Imatinib	Rosuvastatin
Brexpiprazole	Imidapril	Ruxolitinib
Bromazepam	Indometacin	Salazosulfapyridine
Bromocriptine	Irbesartan	Selegiline
Brotizolam	Isoleucine, leucine, valine	Senna leaf/ Powdered senna leaf
Bucolome	Isoniazid	Sennoside
Camostat	Istradefyline	Sertraline
Candesartan	Itraconazole	Simeprevir
Candesartan/ Amlodipine	L-/carbocisteine	Sitafloxacin
Candesartan/ Hydrochlorothiazide combination	Lacosamide	Sodium valproate
Capecitabine	Lactulose	Sofosbuvir
Captopril	Lamotrigine	Solifenacin succinate
Carbamazepine	Lansoprazole	Sorafenib
Carteolol	Lansoprazole/ Amoxicillin/Clarithromycin	Sotalol
Carvedilol	Ledipasvir/Sofosbuvir	Sparfloxacin
Cefcapene	Leflunomide	Spherical carbon aceousad sorbent
Cefdinir	Lenvatinib	Spironolactone

Cefditoren	Levetiracetam	Sulfamethoxazole Trimethoprim
Cefteram	Levocarnitine	Sulpiride
Celecoxib	Levocetirizine	Sunitinib
Celiprolol	Levodopa/Benserazide	Suvorexant
Cetirizine	Levodopa/Carbidopa	Tacrolimus
Chenpi hansatsu	Levodopa/Carbidopa/ Entacapone	Tafamidis meglumine
Chlormadinone	Levofloxacin	Tamsulosin
Chlorpheniramine	Levonorgestrel Ethinylestradiol	Tebipenem
Chlorpromazine	Levothyroxine	Tegafur/Gimeracil/ Oteracil potassium combination
Cibenzoline succinate	Linezolid	Telaprevir
Ciclosporin	Lisinopril	Telithromycin
Cilostazol	Lithium carbonate	Telmisartan
Cimetidine	Lomefloxacin	Telmisartan/ Amlodipine combination
Cinacalcet	Loratadine	Temocapril
Ciprofloxacin	Lorazepam	Temozolomide
Clarithromycin	Lorlatinib	Tenofovir
Clomipramine	Losartan	Terazosin
Clonazepam	Losartan/ Hydrochlorothiazide combination	Terbinafine
Clopidogrel	Loxoprofen	Thalidomide
Cloxazolam	Lubiprostone	Theophylline
Clozapine	Manidipine	Thiamazole
Colchicine	Maprotiline	Thiapride
Colestimide	Mecobalamin	Tiopronin
Component nutrition for liver failure	Memantine	Tipepidine
Crizotinib	Mercaptopurine	Tizanidine
Cyproheptadine	Metenolone	Tofacitinib
Dabigatran	Methadone	Tolvaptan
Daclatasvir	Methotrexate	Topiramate
Daiokanzoto	Methylphenidate	Torasemide
Daisaikoto	Metildigoxin	Tosufloxacin

Dantrolene	Metoclopramide	Tramadol
Deferasirox	Metoprolol	Tramadol/ Acetaminophen combination
Dexamethasone	Metronidazole	Trandolapril
Diazoxide	Mianserin	Trazodone
Diclofenac	Miconazole	Triazolam
Digoxin	Minocycline	Trichlormethiazide
Diltiazem	Mirabegron	Trilostane
Dinoprostone	Mirogabalin	Urapidil
Diphenidol	Mirtazapine	Ursodeoxycholic acid
Disopyramide	Mizoribine	Valaciclovir
Disopyramide	Morphine	Valganciclovir
Distigmine	Mosapride	Valsartan
Disulfiram	Moxifloxacin	Valsartan/ Amlodipine combination
Dolutegravir	Mycophenolate mofetil	Valsartan/ Hydrochlorothiazide combination
domperidone	Nalfurafine	Venlafaxine
Donepezil	Nifedipine	Verapamil
Doxazosin	Nilotinib	Vonoprazan
Dried thyroide	Non-pyrine cold remedy	Vonoprazan/ Amoxicillin/Clarithromycin
Duloxetine	Octotiamine, B2, B6, B12 combination	Voriconazole
Dutasteride	Ofloxacin	Warfarin
Edoxaban	Olanzapine	Zaltoprofen
Elobixibat	Olmesartan	Zolpidem
Emtricitabine/ Tenofovir/Alafenamide	Olmesartan/ Azelnidipine combination	Zopiclone
		Zotepin

Supplementary 2 Table. Number of drugs used during the observation period that have been reported to be associated with hypoglycemia-related hospitalization.

Drugs with reported hypoglycemia	Total	HRH(+)	HRH(-)	P value
Abemaciclib	34	0	34	1.000
Abiraterone	1,048	29	1,019	0.002
Acebutolol	46	2	44	0.147
Acetazolamide	9,002	207	8,795	<0.001
Aciclovir	11,637	224	11,413	<0.001
Acotiamide	4,064	101	3,693	<0.001
Afatinib	344	4	340	0.823
Alendronate	26,449	526	25,923	<0.001
Alfacalcidol	41,886	1,322	40,564	<0.001
Allopurinol	46,092	1,034	45,058	<0.001
Alprazolam	11,210	202	11,008	0.004
Amantadine	5,022	129	4,893	<0.001
Amenamivir	1,291	30	1,261	0.016
Amiodarone	13,571	290	13,281	<0.001
Amitriptyline	4,785	115	4,670	<0.001
Amlodipine	219,276	4,244	215,032	<0.001
Amoxapine	874	19	855	0.091
Amoxicillin	42,277	956	41,321	<0.001
Amoxicillin/Potassium clavulanate	29,174	814	28,360	<0.001
Ampiroxicam	47	2	45	0.153
Antipyretic	18,366	562	17,804	<0.001
Apixaban	23,611	379	23,232	0.092
Aripiprazole	4,158	96	4,062	<0.001
Asenapine	635	18	617	0.012
Aspirin	190,324	3,789	186,535	<0.001
Aspirin/Lansoprazole combination	18,627	366	18,261	<0.001
Atenolol	11,298	207	11,091	0.002
Atorvastatin	96,842	1,630	95,212	<0.001

axitinib	379	8	371	0.282
Azathioprine	2,479	37	2,442	0.944
Azilsartan	46,555	940	45,615	<0.001
Azilsartan/Amlodipine combination	8,039	137	7,902	0.091
Azithromycin	20,106	569	19,537	<0.001
Baloxavir marboxil	855	17	838	0.200
Bepridil	3,374	42	3,332	0.316
Beraprost	7,924	253	7,671	<0.001
Betamethasone/d-chlorpheniramine	6,718	160	6,558	<0.001
Bexarotene	7	0	7	1.000
Bezafibrate	16,858	304	16,554	<0.001
Bisoprolol	73,538	1,184	72,354	0.001
Blonanserin	970	24	946	0.015
Brexpiprazole	150	5	145	0.072
Bromazepam	2,717	63	2,654	<0.001
Bromocriptine	340	7	333	0.360
Brotizolam	119,686	2,676	117,010	<0.001
Bucolome	692	15	677	0.151
Camostat	9,286	313	8,973	<0.001
Candesartan	55,664	1,149	54,515	<0.001
Candesartan/Amlodipine	7,522	138	7,384	0.009
Candesartan/Hydrochlorothiazide combination	3,734	88	3,646	<0.001
Capecitabine	5,783	74	5,709	0.230
Captopril	2,435	31	2,404	0.445
Carbamazepine	7,185	191	6,994	<0.001
Carteolol	5,141	172	4,969	<0.001
Carvedilol	82,184	1,839	80,345	<0.001
Cefcapene	111,743	2,667	109,076	<0.001
Cefdinir	50,583	1,144	49,439	<0.001
Cefditoren	26,060	683	25,377	<0.001
Cefteram	2,594	77	2,517	<0.001
Celecoxib	96,086	1,861	94,225	<0.001
Celiprolol	837	17	820	0.193
Cetirizine	4,072	120	3,952	<0.001

Chenpi hansatsu	1,060	30	1,030	0.001
Chlormadinone	2,224	69	2,155	<0.001
Chlorpheniramine	11,988	295	11,693	<0.001
Chlorpromazine	8,154	212	7,942	<0.001
Cibenzoline succinate	4,546	93	4,453	0.002
Ciclosporin	4,529	85	4,444	0.027
Cilostazol	54,856	1,340	53,516	<0.001
Cimetidine	4,050	73	3,977	0.085
Cinacalcet	4,917	268	4,649	<0.001
Ciprofloxacin	4,219	111	4,108	<0.001
Clarithromycin	53,288	1,378	51,910	<0.001
Clomipramine	754	14	740	0.362
Clonazepam	11,546	318	11,228	<0.001
Clopidogrel	110,705	2,182	108,523	<0.001
Cloxazolam	819	21	798	0.019
Clozapine	8	0	8	1.000
Colchicine	1,652	34	1,618	0.047
Colestimide	790	21	769	0.011
Component nutrition for liver failure	5,652	204	5,448	<0.001
Crizotinib	56	0	56	1.000
Cyproheptadine	1,446	48	1,398	<0.001
Dabigatran	7,527	113	7,414	0.853
Daclatasvir	709	11	698	0.756
Daiokanzoto	3,955	132	3,823	<0.001
Daisaikoto	218	4	214	0.568
Dantrolene	990	24	966	0.023
Deferasirox	786	16	770	0.182
Dexamethasone	40,652	805	39,847	<0.001
Diazoxide	17	5	12	<0.001
Diclofenac	173,219	3,451	169,768	<0.001
Digoxin	17,768	412	17,356	<0.001
Diltiazem	27,345	516	26,829	<0.001
Dinoprostone	204	3	201	1.000
Diphenidol	10,472	270	10,202	<0.001
Disopyramide	937	25	912	0.006

Disopyramide	2,673	53	2,620	0.032
Distigmine	13,055	396	12,659	<0.001
Disulfiram	100	9	91	<0.001
Dolutegravir	44	0	44	1.000
domperidone	51,699	1,473	50,226	<0.001
Donepezil	22,635	676	21,959	<0.001
Doxazosin	31,953	1,037	30,916	<0.001
Dried thyroide	70	4	66	0.020
Duloxetine	19,011	408	18,603	<0.001
Dutasteride	12,524	234	12,290	<0.001
Edoxaban	28,480	370	28,110	0.013
Elobixibat	2,279	58	2,221	<0.001
Emtricitabine/Tenofovir/Alafenamide	27	0	27	1.000
Enalapril	39,988	889	39,099	<0.001
Entacapone	607	11	591	0.495
Enteral nutrition	40,265	1,232	39,033	<0.001
Enzalutamide	1,338	32	1,306	0.006
Erlotinib	705	17	688	0.057
Erythromycin	862	28	834	<0.001
Escitalopram	2,810	54	2,756	0.055
Ethambutol	2,352	61	2,291	<0.001
Etizolam	52,360	1,145	51,215	<0.001
Etodolac	11,232	296	10,936	<0.001
Etretinate	507	8	499	0.852
Everolimus	823	13	810	0.771
Exemestane	898	9	889	0.329
Ezetimibe	32,302	510	31,792	0.112
Famotidine	167,773	3,378	164,395	<0.001
Faropenem	5,715	170	5,545	<0.001
febuxostat	83,669	1,878	81,791	<0.001
Fenofibrate	11,022	153	10,869	0.472
Fesoterodine	5,039	88	4,951	0.110
Flavoxate	2,536	71	2,465	<0.001
Flecainide	2,089	26	2,063	0.463
Fluconazole	7,925	157	7,768	<0.001

Flunitrazepam	41,574	989	40,585	<0.001
fluvastatin	4,864	108	4,756	<0.001
fluvoxamine	2,216	44	2,172	0.047
Forodesine	42	2	40	0.127
Fosfomycin calcium	6,189	215	5,974	<0.001
Furosemide	205,963	5,436	200,527	<0.001
Fursultiamine	6,386	196	6,390	<0.001
Gabapentin	1,058	24	1,034	0.040
Galantamine	5,054	131	4,923	<0.001
Garenoxacin	21,032	560	20,472	<0.001
Gatifloxacin	19,852	412	19,440	<0.001
Gefitinib	752	15	737	0.224
Glecaprevir/Pibrentasvir	656	15	641	0.101
Guanfacine	3	0	3	1.000
Haloperidol	63,380	1,816	61,564	<0.001
Hydrocortisone	3,069	139	2,930	<0.001
Hydroxycarbamide	888	11	877	0.676
Hydroxychloroquine	248	0	248	0.057
Imatinib	528	12	516	0.143
Imidapril	18,542	472	18,070	<0.001
Indometacin	465	8	457	0.564
Irbesartan	17,556	428	17,128	<0.001
Isoleucine, leucine, valine	11,603	351	11,252	<0.001
Isoniazid	4,229	96	4,133	<0.001
Istradefyline	555	12	543	0.212
Itraconazole	6,072	138	5,934	<0.001
L-/carbocisteine	109,406	2,654	106,752	<0.001
Lacosamide	670	17	653	0.034
Lactulose	11,248	395	10,853	<0.001
Lamotrigine	1,019	24	995	0.026
Lansoprazole	208,023	4,249	203,774	<0.001
Lansoprazole/Amoxicillin/Clarithromycin	4,838	81	4,757	0.254
Ledipasvir/Sofosbuvir	962	15	947	0.788
Leflunomide	91	1	90	1.000
Lenvatinib	799	9	790	0.555

Levetiracetam	11,351	250	11,101	<0.001
Levocarnitine	1,121	68	1,053	<0.001
Levocetirizine	18,267	362	17,905	<0.001
Levodopa/Benserazide	2,464	60	2,404	<0.001
Levodopa/Carbidopa	6,306	149	6,157	<0.001
Levodopa/Carbidopa/Entacapone	408	4	404	0.538
Levofloxacin	211,570	4,848	206,722	<0.001
Levonorgestrel Ethinylestradiol	2	0	2	1.000
Levothyroxine	27,570	756	26,814	<0.001
Linezolid	4,090	132	3,958	<0.001
Lisinopril	2,588	56	2,532	0.004
Lithium carbonate	1,443	28	1,415	0.149
Lomefloxacin	405	18	387	<0.001
Loratadine	8,953	252	8,701	<0.001
Lorazepam	7,739	164	7,575	<0.001
Lorlatinib	11	0	11	1.000
Losartan	29,435	653	28,782	<0.001
Losartan/Hydrochlorothiazide combination	7,724	188	7,536	<0.001
Loxoprofen	325,924	5,804	320,120	<0.001
Lubiprostone	33,874	1,074	32,800	<0.001
Manidipine	1,222	28	1,194	0.019
Maprotiline	726	15	711	0.213
Mecobalamin	95,795	2,080	93,715	<0.001
Memantine	10,489	312	10,177	<0.001
Mercaptopurine	201	4	197	0.547
Metenolone	975	27	948	0.002
Methadone	97	3	94	0.173
Methotrexate	7,670	112	7,558	0.956
Methylphenidate	51	3	48	0.040
Metildigoxin	5,477	103	5,374	0.014
Metoclopramide	190,201	4,297	185,904	<0.001
Metoprolol	18,245	272	17,973	0.856
Metronidazole	15,679	481	15,198	<0.001
Mianserin	5,507	143	5,364	<0.001
Miconazole	4,252	114	4,138	<0.001

Minocycline	31,040	955	30,085	<0.001
Mirabegron	19,372	331	19,041	0.007
Mirogabalin	551	11	540	0.286
Mirtazapine	7,764	165	7,599	<0.001
Mizoribine	1,668	27	1,641	0.620
Morphine	2,027	36	1,991	0.267
Mosapride	60,735	1,657	59,078	<0.001
Moxifloxacin	35,482	851	34,631	<0.001
Mycophenolate mofetil	1,369	21	1,348	0.836
Nalfurafine	5,113	235	4,878	<0.001
Nifedipine	102,650	2,579	100,071	<0.001
Nilotinib	171	6	165	0.042
Non-pyrine cold remedy	81,376	2,529	78,847	<0.001
Octotiamine, B2, B6, B12 combination	2,285	55	2,230	<0.001
Ofloxacin	61,966	1,402	60,564	<0.001
Olanzapine	2,851	44	2,807	0.764
Olmesartan	67,741	1,516	66,225	<0.001
Olmesartan/Azelnidipine combination	10,207	227	9,980	<0.001
Ombitasvir/Paritaprevir/Ritonavir	130	4	126	0.127
Omeprazole	20,705	573	20,132	<0.001
Oseltamivir	15,812	562	15,250	<0.001
Oxycodone	22,337	463	21,874	<0.001
Palbociclib	192	1	191	0.538
Paliperidone	322	5	317	0.815
Paroxetine	6,545	149	6,396	<0.001
Pazopanib	367	6	361	0.666
Pergolide	87	1	86	1.000
Perospirone	4,541	140	4,401	<0.001
Phenytoin	2,555	69	2,486	<0.001
Phytonadione	893	24	869	0.005
Picosulfate	184,432	4,039	180,393	<0.001
Pilsicainide	9,191	152	9,039	0.149
Polycarbophil calcium	5,085	177	4,908	<0.001
Pramipexole	2,742	74	2,668	<0.001
Pranlukast	7,466	197	7,269	<0.001

Precipitated calcium carbonate	18,416	846	17,570	<0.001
Prednisolone	76,792	1,465	75,327	<0.001
Pregabalin	76,756	1,502	75,254	<0.001
Probenecid	207	4	203	0.554
Promethazine	129	2	127	0.716
Propafenone	1,049	26	1,023	0.014
Propranolol	7,589	149	7,440	<0.001
Propylthiouracil	429	5	424	0.840
Prulifloxacin	1,083	35	1,048	<0.001
Pyrazinamide	782	23	759	0.002
Quetiapine	7,880	163	7,717	<0.001
Rabeprazole	89,239	1,915	87,324	<0.001
Rabeprazole/Amoxicillin/Clarithromycin	2,026	33	1,993	0.527
Raloxifene	4,333	83	425	0.017
Ramelteon	32,567	866	31,701	<0.001
Regorafenib	776	16	760	0.177
Ribavirin	1,141	21	112	0.325
Rifampicin	4,553	138	4,415	<0.001
Rifaximin	1,127	344	1,093	<0.001
Risperidone	46,477	1,487	44,990	<0.001
Ritodrine	833	6	827	0.082
Rivaroxaban	17,615	247	17,368	0.446
Ropinirole	814	25	789	0.001
Rosuvastatin	119,338	1,729	117,609	0.429
Ruxolitinib	98	1	97	1.000
Salazosulfapyridine	4,263	89	4,174	0.001
Selegiline	1,052	25	1,027	0.021
Senna leaf/Powdered senna leaf	40,308	875	39,433	<0.001
Sennoside	330,694	6,579	324,115	<0.001
Sertraline	3,568	81	3,487	<0.001
Simeprevir	193	4	189	0.375
Sitafloxacin	6,513	152	6,361	<0.001
Sodium valproate	11,447	295	11,152	<0.001
Sofosbuvir	576	12	564	0.222
Solifenacin succinate	16,438	355	16,083	<0.001

Sorafenib	1,595	51	1,544	<0.001
Sotalol	561	8	553	1.000
Sparfloxacin	2	0	2	1.000
Spherical carbon aceousad sorbent	14,685	671	14,014	<0.001
Spironolactone	87,598	2,399	85,259	<0.001
Sulfamethoxazole Trimethoprim	40,759	803	39,956	<0.001
Sulpiride	10,712	261	10,451	<0.001
Sunitinib	524	13	511	0.067
Suvorexant	42,345	1,002	41,343	<0.001
Tacrolimus	7,219	123	7,096	0.103
Tafamidis meglumine	9	0	9	1.000
Tamsulosin	36,110	792	35,318	<0.001
Tebipenem	9	0	9	1.000
Tegafur/Gimeracil/Oteracil potassium combination	18,002	434	17,568	<0.001
Telaprevir	65	1	64	0.619
Telithromycin	1	0	1	1.000
Telmisartan	71,642	1,569	70,073	<0.001
Telmisartan/Amlodipine combination	16,920	344	16,576	<0.001
Temocapril	3,564	83	3,481	<0.001
Temozolomide	435	4	431	0.428
Tenofovir	216	5	211	0.256
Terazosin	342	14	328	0.001
Terbinafine	30,878	970	29,908	<0.001
Thalidomide	152	5	147	0.076
Theophylline	14,309	369	13,940	<0.001
Thiamazole	3,807	59	3,748	0.693
Thiapride	8,836	252	8,584	<0.001
Tiopronin	126	4	122	0.117
Tipepidine	11,754	417	11,337	<0.001
Tizanidine	7,453	175	7,278	<0.001
Tofacitinib	152	0	152	0.180
Tolvaptan	34,234	1,014	33,220	<0.001
Topiramate	250	9	241	0.013
Torasemide	19,656	679	18,977	<0.001

Tosufloxacin	4,448	126	4,322	<0.001
Tramadol	24,962	528	2,434	<0.001
Tramadol/Acetaminophen combination	41,720	884	40,836	<0.001
Trandolapril	1,163	22	1,141	0.222
Trazodone	18,139	443	17,696	<0.001
Triazolam	19,895	525	19,370	<0.001
Trichlormethiazide	35,579	919	34,660	<0.001
Trilostane	8	0	8	1.000
Urapidil	13,723	408	13,315	<0.001
Ursodeoxycholic acid	63,305	1,370	61,935	<0.001
Valaciclovir	12,935	269	12,666	<0.001
Valganciclovir	1,441	25	1,416	0.387
Valsartan	46,221	1,107	45,114	<0.001
Valsartan/Amlodipine combination	8,694	157	8,537	0.011
Valsartan/Hydrochlorothiazide combination	2,635	62	2,573	<0.001
Venlafaxine	362	4	358	0.825
Verapamil	33,077	734	32,343	<0.001
Vonoprazan	69,676	1,166	68,510	<0.001
Vonoprazan/Amoxicillin/Clarithromycin	5,705	57	5,648	0.003
Voriconazole	2,871	61	2,810	0.005
Warfarin	59,123	1,256	57,867	<0.001
Zaltoprofen	3,469	91	3,378	<0.001
Zolpidem	118,870	2,713	116,157	<0.001
Zopiclone	36,302	958	35,344	<0.001
Zotepin	712	25	687	<0.001

Supplementary Table 3. Logistic regression analysis of predictors of hypoglycemia related-hospitalization by individual components of the hypoglycemic agents.

		HRH (+)			
	Total	n(%)	OR	95%CI	P value
Biguanides					
Buformin	1,457	40(2.7)	1.39	1.00-1.92	0.048
Metformin	202,857	2585(1.3)	0.72	0.69-0.76	<0.001
DPP-4 inhibitors					
Alogliptin	52,815	791(1.5)	0.96	0.89-1.03	0.265
Anagliptin	7,181	98(1.4)	0.90	0.73-1.10	0.293
Linagliptin	121,619	2755(2.3)	1.62	1.55-1.69	<0.001
Omarigliptin	3,106	60(1.9)	1.31	1.01-1.69	0.045
Saxagliptin	12,120	181(1.5)	1.03	0.89-1.19	0.711
Sitagliptin	215,539	3240(1.5)	1.05	1.01-1.10	0.023
Teneligliptin	66,830	1215(1.8)	1.23	1.16-1.31	<0.001
Trelaglyptin	3,263	37(1.1)	0.83	0.60-1.15	0.260
Vildagliptin	104,521	1967(1.9)	1.29	1.23-1.36	<0.001
Glinides					
Mitiglinide	48,467	1235(2.5)	1.19	1.12-1.27	<0.001
Nateglinide	10,630	279(2.6)	1.38	1.22-1.56	<0.001
Repaglinide	32,503	825(2.5)	1.16	1.08-1.25	<0.001
GLP-1 RA					
Dulaglutide	16,905	451(2.7)	1.34	1.21-1.48	<0.001
Exenatide	2,303	52(2.3)	1.16	0.87-1.54	0.321
Liraglutide	15,840	424(2.7)	1.59	1.44-1.77	<0.001
Lixisenatide	1,681	38(2.3)	1.19	0.86-1.66	0.291
Insulin					
	445,129	8910(2.0)	3.44	3.25-3.64	<0.001
SGLT2 inhibitors					
Canagliflozin	10,470	82(0.8)	0.54	0.43-0.67	<0.001
Dapagliflozin	17,286	174(1.0)	0.68	0.59-0.80	<0.001
Empagliflozin	25,750	264(1.0)	0.65	0.58-0.74	<0.001
Ipragliflozin	16,053	180(1.1)	0.80	0.69-0.93	0.004
Luseogliflozin	5,141	68(1.3)	0.90	0.71-1.15	0.404
Tofogliflozin	7,824	82(1.0)	0.71	0.56-0.88	0.002
Sulfonylureas					

Acetohexamide	99	5(5.1)	3.64	1.44-9.20	0.006
Chlorpropamide	9	0(0)	-	-	-
Glibenclamide	14,613	615(4.2)	2.72	2.49-2.96	<0.001
Gliclazide	26,059	463(1.8)	0.98	0.89-1.07	0.615
Glimepiride	164,128	3588(2.2)	1.58	1.52-1.66	<0.001
Glyclopyramide	11	1(9.1)	8.21	0.98-68.84	0.052
Tolbutamide	95	0(0)	-	-	-
Thiazolidine					
Pioglitazone	65,736	1383(2.1)	1.35	1.27-1.44	<0.001
α-GI					
Acarbose	12,401	354(2.9)	1.53	1.37-1.70	<0.001
Miglitol	53,228	1337(2.5)	1.41	1.32-1.49	<0.001
Voglibose	104,217	2502(2.4)	1.47	1.40-1.55	<0.001

Supplementary Table 4. Logistic regression analysis for predictors of hypoglycemia-related hospitalization among drugs for which hypoglycemia was reported.

Concomitant medication	OR	95% CI	p-value
Acetazolamide	1.17	1.01-1.35	0.042
Alfacalcidol	1.23	1.15-1.32	<0.001
Amoxicillin/potassium clavulanate	1.25	1.16-1.36	<0.001
Antipyretic	1.11	1.01-1.22	0.031
Aspirin	1.1	1.05-1.16	<0.001
Beraprost	1.14	1.00-1.31	0.046
Bezafibrate	1.23	1.10-1.39	0.001
Camostat	1.51	1.34-1.70	<0.001
Candesartan	1.1	1.03-1.18	0.003
Carteolol	1.61	1.37-1.89	<0.001
Cefcapene	1.16	1.10-1.22	<0.001
Cefditoren	1.13	1.04-1.23	0.003
Cetirizine	1.25	1.04-1.52	0.02
Chlormadinone	1.37	1.06-1.76	0.016
Cilostazol	1.11	1.04-1.18	0.001

Cinacalcet	1.57	1.36-1.82	<0.001
Clarithromycin	1.1	1.03-1.17	0.007
Component nutrition for liver failure	1.29	1.08-1.54	0.005
Diazoxide	15.49	4.87-49.31	<0.001
Diphenidol	1.15	1.01-1.31	0.03
Distigmine	1.18	1.05-1.32	0.004
Disulfiram	4.21	2.05-8.62	<0.001
Domperidone	1.18	1.11-1.26	<0.001
Donepezil	1.39	1.27-1.52	<0.001
Doxazosin	1.17	1.09-1.27	<0.001
Duloxetine	1.13	1.01-1.25	0.032
Enalapril	1.17	1.08-1.26	<0.001
Enteral nutrition	1.17	1.10-1.25	<0.001
Etodolac	1.24	1.09-1.40	0.001
Fosfomycin calcium	1.21	1.05-1.40	0.01
Furosemide	1.5	1.43-1.58	<0.001
Fursultiamine	1.35	1.16-1.56	<0.001
Haloperidol	1.17	1.10-1.24	<0.001

Hydrocortisone	2.03	1.70-2.44	<0.001
Imidapril	1.2	1.09-1.32	<0.001
Irbesartan	1.21	1.09-1.34	<0.001
Levocarnitine	1.38	1.06-1.80	0.016
Levofloxacin	1.18	1.13-1.24	<0.001
Levothyroxine	1.22	1.13-1.32	<0.001
Losartan	1.12	1.03-1.22	0.007
Losartan/hydrochlorothiazide combination	1.23	1.05-1.43	0.009
Lubiprostone	1.19	1.11-1.28	<0.001
Mecobalamin	1.12	1.06-1.18	<0.001
Memantine	1.2	1.05-1.36	0.005
Methylphenidate	5.15	1.53-17.28	0.008
Metoclopramide	1.15	1.10-1.20	<0.001
Metronidazole	1.21	1.10-1.33	<0.001
Minocycline	1.18	1.10-1.27	<0.001
Mosapride	1.13	1.07-1.20	<0.001
Moxifloxacin	1.16	1.07-1.26	<0.001
Nifedipine	1.11	1.06-1.17	<0.001

Non-pyrine cold remedy	1.42	1.35-1.50	<0.001
Olmesartan	1.15	1.08-1.22	<0.001
Omeprazole	1.15	1.05-1.26	0.003
Oseltamivir	1.32	1.20-1.44	<0.001
Picosulfate	1.06	1.01-1.11	0.01
Polycarbophil calcium	1.26	1.08-1.48	0.004
Precipitated calcium carbonate	1.41	1.28-1.55	<0.001
Prulifloxacin	1.47	1.04-2.08	0.031
Risperidone	1.36	1.28-1.45	<0.001
Sennoside	1.1	1.05-1.15	<0.001
Sorafenib	1.35	1.01-1.81	0.045
Spherical carbonaceous adsorbent	1.44	1.32-1.58	<0.001
Spironolactone	1.13	1.06-1.19	<0.001
Tamsulosin	1.11	1.03-1.21	0.008
Tegafur/gimeracil/oteracil potassium combination	1.19	1.07-1.33	0.001
Telmisartan	1.15	1.09-1.23	<0.001
Terbinafine	1.3	1.21-1.39	<0.001
Tipepidine	1.39	1.25-1.55	<0.001

Torasemide	1.29	1.19-1.41	<0.001
Triazolam	1.16	1.06-1.28	0.002
Valsartan	1.22	1.14-1.30	<0.001
Zopiclone	1.13	1.05-1.21	0.001

OR, odds ratio; 95% CI, 95% confidence interval.