SUPPLEMENTARY INFORMATION

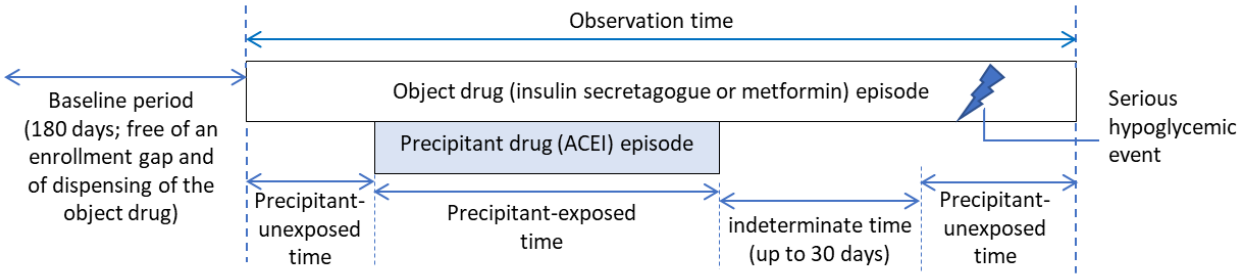

Figure S1. Observation time

ACEI: angiotensin-converting enzyme inhibitor. Observation time, in which at least one outcome (serious hypoglycemia) occurrence was required, was constructed for each object drug separately. An object drug episode began at the first dispensing date of that episode and ended by end of days' supply of the episode (including a 7-day grace period), Medicaid enrollment discontinuation, or end of dataset, whichever occurred first. A precipitant drug episode was allowed to begin on, before, or after the start date of the object drug episode. More than one precipitant drug episode was allowed within an object drug's observation time. Indeterminate time lasted up to 30 days, or until another prescription for the precipitant was dispensed. We performed a sensitivity analysis that included observation time censored by death.

Table S1. Validated algorithm to ascertain serious hypoglycemia outcome

Description		ICD-9-CM code	Diagnosis code position and claims type	Validation statistics
Hypoglycemic coma		251.0	Any position of discharge diagnosis in ED claim or principal position in inpatient claim	PPV ~89%[22] (ED claim); 78%[23] (inpatient claim)
Other specific hypoglycemia		251.1		
Hypoglycemia, unspecified		251.2		
Diabetes with other specified manifestations		250.8X		
Exclusionary diagnosis codes in the occurrences of 250.8X[22,23]				
Secondary diabetic glycogenosis	Other specified endocrine disorders	259.8		
Diabetic lipidosis	Mixed hyperlipidemia	272.7		
Cellulitis	Cellulitis and abscess of finger and toe	681.XX		
	Other cellulitis and abscess	682.XX		
	Unspecified local infection of skin and subcutaneous tissue	686.9		
Ulcers of the lower extremity	Ulcer of lower limbs, except decubitus ulcer	707.1X		
	Pressure ulcer stages	707.2X		
	Chronic ulcer of other specified sites	707.8		
	Chronic ulcer of unspecified site	707.9		
Necrobiosis lipoidica diabeticorum	Degenerative skin disorders	709.3		
Osteomyelitis	Acute osteomyelitis	730.0X		
	Chronic osteomyelitis	730.1X		
	Unspecified osteomyelitis	730.2X		
	Other bone involvement in diseases classified elsewhere	731.8		

ED: emergency department. ICD-9-CM: International Classification of Diseases, 9th Revision, Clinical Modification. PPV: positive predictive value.

Table S2. Time-varying potential confounders controlled for using conditional Poisson regression model

Drugs that may be associated with hypoglycemia*	
Anti-infectives†	alatrofloxacin, cinoxacin, ciprofloxacin, chloramphenicol, chloroquine, enoxacin, gatifloxacin, gemifloxacin, grepafloxacin, levofloxacin, lomefloxacin, moxifloxacin, nalidixic acid, norfloxacin, ofloxacin, pentamidine, quinine, sparfloxacin, sulfamethoxazole, trimethoprim, trovafloxacin
ARBs‡	losartan, candesartan, valsartan, irbesartan, eprosartan, olmesartan, telmisartan, azilsartan
Beta blockers‡	acebutolol, atenolol, betaxolol, bisoprolol, carteolol, labetalol, metoprolol, nadolol, nebivolol, penbutolol, pindolol, propranolol, sotalol, timolol
Calcium channel blockers‡	amlodipine, diltiazem, felodipine, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine, verapamil
Salicylates‡	aminosalicylic acid, aspirin, bismuth subsalicylate, choline salicylate, magnesium salicylate, magnesium salicylate tetrahydrate, phenyl salicylate, salicylic acid, salsalate, sodium salicylate, sodium thiosalicylate
Others‡	haloperidol, quinidine, clofibrate, disopyramide
Drugs that may be associated with hyperglycemia*	
Atypical antipsychotics‡	aripiprazole, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone
Calcineurin inhibitors‡	cyclosporine, sirolimus, tacrolimus
Corticosteroids‡	betamethasone, budesonide, cortisone, dexamethasone, fluodrocortisone, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone
Protease inhibitors‡	amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir
Furosemide‡	furosemide
Thiazide and thiazide-like diuretics‡	bendroflumethiazide, benzthiazide, chlorothiazide, chlorthalidone, hydrochlorothiazide, hydroflumethiazide, indapamide, methyclothiazide, metolazone, polythiazide, trichlormethiazide
Drugs that may interact with insulin secretagogues*	
CYP2C9 inhibitors	amiodarone‡, capecitabine‡, cotrimoxazole†, efavirenz‡, fenofibrate‡, fluconazole†, isoniazid‡, lovastatin‡, metronidazole†, miconazole†, oxandrolone‡, paroxetine‡, probenecid‡, sulfamethoxazole†, sulfinpyrazone‡, teniposide‡, tigecycline‡, voriconazole†, zafirlukast‡
CYP3A4 inhibitors	azithromycin†, clarithromycin†, erythromycin†, simvastatin‡, gemfibrozil‡
Insulin‡	insulin
Other non-insulin antidiabetes drugs‡	acarbose, exenatide, linagliptin, pioglitazone, pramlintide, rosiglitazone, saxagliptin
Major non-chronic condition that may be associated with hypoglycemia§	
Acute infection†	Acute infection identified by discharge diagnosis codes appearing at any position in inpatient or outpatient claims
Others‖	Age, nursing home residence status, Medicaid-Medicare dual-enrollment status, concomitant metformin use when the object drug was an insulin secretagogue

ARB: angiotensin II receptor blockers. CYP: cytochrome P450 enzyme. *Identified by National Drug Codes, dispensing date, and days' supply. †Measured as a person-day level binary variable indicating being dispensed or diagnosed on the current day or any time during the 15 days prior to the current day. ‡Measured as a person-day level binary variable indicating being dispensed on the current day (refers to each day during the observation time as current) or any time during the 30 days prior to the current day. §Identified by International Classification of Diseases, 9th Revision, Clinical Modification diagnosis codes, and admission or service date. ‖Measured on the current day; binary variables except for age (continuous variable).

Table S3. ICD-9-CM diagnosis codes used to identify acute infections

ICD-9-CM code	Description
001.*	Cholera
002.*	Typhoid and paratyphoid fevers
003.*	Other salmonella infections
004.*	Shigellosis
005.*	Other food poisoning (bacterial)
006.*, except 006.1	Amebiasis
007.*	Other protozoal intestinal diseases
008.*	Intestinal infections due to other organisms
009.*	Ill-defined intestinal infections
018.0*	Miliary tuberculosis
020.*	Plague
021.*	Tularemia
022.*	Anthrax
023.*	Brucellosis
024	Glanders
025	Melioidosis
026.*	Rat-bite fever
027.*	Other zoonotic bacterial diseases
030.*	Leprosy
031.*	Diseases due to other mycobacteria
032.*	Diphtheria
033.*	Whooping cough
034.*	Streptococcal sore throat and scarlet fever
035	Erysipelas
036.*	Meningococcal infection
037	Tetanus
038.*	Septicemia
039.*, except 039.4	Actinomycotic infections
040.*, except 040.1	Other bacterial diseases
041.*, except 041.81	Bacterial infection in conditions classified elsewhere and of unspecified site
045.*	Acute poliomyelitis
047.*	Meningitis due to enterovirus
048	Other enterovirus diseases of central nervous system
049.*	Other non-arthropod-borne viral diseases of central nervous system
050.*	Smallpox
051.*	Cowpox and paravaccinia
052.*	Chickenpox
053.*, except 053.12, 053.13	Herpes zoster
054.*	Herpes simplex
055.*	Measles
056.*	Rubella
057.*	Other viral exanthemata
058.*	Other human herpesvirus
059.*	Other poxvirus infections
060.*	Yellow fever
061	Dengue
062.*	Mosquito-borne viral encephalitis
063.*	Tick-borne viral encephalitis

ICD-9-CM code	Description
064	Viral encephalitis transmitted by other and unspecified arthropods
065.*	Arthropod-borne hemorrhagic fever
066.*	Other arthropod-borne viral diseases
070.*, except 070.22, 070.23, 070.32, 070.33, 070.44, 070.54	Viral hepatitis
071	Rabies
072.*	Mumps
073.*	Ornithosis
074.*	Specific diseases due to coxsackie virus
075	Infectious mononucleosis
076.*	Trachoma
077.*	Other diseases of conjunctiva due to viruses and chlamydiae
078.*	Other diseases due to viruses and chlamydiae
079.*, except 079.51, 079.52, 079.53	Viral and chlamydial infection in conditions classified elsewhere and of unspecified site
080	Louse-borne (epidemic) typhus
081.*	Other typhus
082.*	Tick-borne rickettsioses
083.*	Other rickettsioses
084.*	Malaria
085.*	Leishmaniasis
086.*	Trypanosomiasis
087.*	Relapsing fever
088.*	Other arthropod-borne diseases
090.*	Congenital syphilis
091.*	Early syphilis symptomatic
092.*	Early syphilis latent
093.*	Cardiovascular syphilis
094.*	Neurosyphilis
095.*	Other forms of late syphilis with symptoms
096	Late syphilis, latent
097.*	Other and unspecified syphilis
098.*, except 098.2, 098.3*	Gonococcal infections
099.*	Other venereal diseases
100.*	Leptospirosis
101	Vincent's angina
103.*	Pinta
104.*	Other spirochetal infection
110.*	Dermatophytosis
111.*	Dermatomycosis other and unspecified
112.*	Candidiasis
114.*, except 114.4	Coccidioidomycosis
115.*	Histoplasmosis
116.*, except 116.2	Blastomycotic infection
118	Opportunistic mycoses
121.*	Other trematode infections
122.*	Echinococcosis
123.*	Other cestode infection
124	Trichinosis

ICD-9-CM code	Description
125.*	Filarial infection and dracontiasis
126.*	Ancylostomiasis and necatoriasis
127.*	Other intestinal helminthiases
128.*	Other and unspecified helminthiases
129	Intestinal parasitism, unspecified
130.*	Toxoplasmosis
131.*	Trichomoniasis
132.*	Pediculosis and phthirus infestation
133.*	Acariasis
134.*	Other infestation
135	Sarcoidosis
136.*	Other and unspecified infectious and parasitic diseases
320.*	Bacterial meningitis
321.*	Meningitis due to other organisms
322.*	Meningitis of unspecified cause
323.*	Encephalitis myelitis and encephalomyelitis
460	Acute nasopharyngitis [common cold]
461.*	Acute sinusitis
462	Acute pharyngitis
463	Acute tonsillitis
464.*	Acute laryngitis and tracheitis
465.*	Acute upper respiratory infections of multiple or unspecified sites
466.*	Acute bronchitis and bronchiolitis
480.*	Viral pneumonia
481	Pneumococcal pneumonia [Streptococcus pneumoniae pneumonia]
482.*	Other bacterial pneumonia
483.*, except 483.0	Pneumonia due to other specified organism
484.*	Pneumonia in infectious diseases classified elsewhere
485	Bronchopneumonia, organism unspecified
486	Pneumonia, organism unspecified
487.*	Influenza
488.*	Influenza due to certain identified influenza viruses
590.1*	Acute pyelonephritis
595.0	Acute cystitis
598.0*	Urethral stricture due to infection
599.0	Urinary tract infection, site not specified

ICD-9-CM: International Classification of Diseases, 9th Revision, Clinical Modification

Table S4. Sensitivity analysis: Rate ratios of serious hypoglycemia occurrence from the use of insulin secretagogues or metformin with versus without concomitant use of angiotensin-converting enzyme inhibitors, including observation time censored by death

Object drug	Precipitant-exposed time* during observation time		Precipitant-unexposed time during observation time		Rate ratio† of serious hypoglycemia	95% CI
	Person-days	Number of serious hypoglycemia occurrences	Person-days	Number of serious hypoglycemia occurrences		
glimepiride	646,667	3,655	906,544	4,742	1.22	1.10, 1.36
glipizide	1,159,194	6,646	1,516,448	8,299	1.09	1.01, 1.17
glyburide	772,044	4,995	1,069,970	6,548	1.06	0.97, 1.16
nateglinide	74,624	691	133,396	944	0.75	0.58, 0.97
repaglinide	153,893	1,292	216,310	1,679	1.15	0.95, 1.41
metformin	4,117,449	15,401	4,650,250	17,588	1.01	0.96, 1.06

CI: confidence interval (based on a two-tailed test). *Precipitant-exposed time: days of concomitant use with a precipitant drug (angiotensin-converting enzyme inhibitor) during observation time since the initiation of the concomitant use. †Rate ratio: [(outcome occurrence rate during precipitant-exposed time)/(outcome occurrence rate during precipitant-unexposed time)]; confounder-adjusted.

Table S5. Sensitivity analysis: Rate ratios of serious hypoglycemia occurrence from the use of insulin secretagogues or metformin with versus without concomitant use of angiotensin-converting enzyme inhibitors, excluding observation time with potentially incomplete data

Object drug	Precipitant-exposed time* during observation time		Precipitant-unexposed time during observation time		Rate ratio† of serious hypoglycemia	95% CI
	Person-days	Number of serious hypoglycemia occurrences	Person-days	Number of serious hypoglycemia occurrences		
glimepiride	374,834	2,192	525,836	2,853	1.18	1.03, 1.35
glipizide	574,171	3,570	775,037	4,419	1.05	0.94, 1.17
glyburide	431,881	2,947	615,082	3,827	1.06	0.94, 1.19
nateglinide	48,181	502	93,645	662	0.78	0.57, 1.06
repaglinide	89,588	836	128,675	1,057	1.33	1.04, 1.70
metformin	1,965,913	7,592	2,361,409	9,131	1.02	0.95, 1.09

CI: confidence interval (based on a two-tailed test). *Precipitant-exposed time: days of concomitant use with a precipitant drug (angiotensin-converting enzyme inhibitor) during observation time since the initiation of the concomitant use. †Rate ratio: [(outcome occurrence rate during precipitant-exposed time)/(outcome occurrence rate during precipitant-unexposed time)]; confounder-adjusted.