Supplementary Online Appendix

Zullo et al. Comparative Safety of Dipeptidyl Peptidase-4 Inhibitors and Sulfonylureas among Frail Older Adults. *Journal of the American Geriatrics Society*.

Supplementary Table S1. Summary of the Protocol of the Hypothetical Target Trial Emulated to Compare Dipeptidyl Peptidase-4 Inhibitors and Sulfonylureas among Older Nursing Home Residents.

Protocol Component	Description
Eligibility criteria	Nursing home residents aged ≥65 years who reside in the nursing home for >100 days. Exclude residents who are comatose, paralyzed, have cancer, or are in hospice.
Treatment strategies	Recommendation to begin second-line glucose-lowering therapy with a dipeptidyl peptidase-4 inhibitor or sulfonylurea drug after a washout of 6 months or longer for the newly initiated agent.
Assignment procedures	Unblinded random assignment to treatments.
Follow-up period	Starts at randomization; ends at the occurrence of an outcome event, loss to follow-up, death, one year of follow-up, or on December 31, 2010, whichever is earlier.
Outcomes[1]	Hypoglycemia, hyperglycemia, acute myocardial infarction, heart failure, composite of major adverse cardiovascular events (acute myocardial infarction, stroke, intracerebral hemorrhage, or subarachnoid hemorrhage) plus heart failure, all-cause mortality
Causal contrasts	Intention-to-treat causal effect (effect of assignment to treatment at baseline) expressed as a marginal hazard ratio.
Analysis plan	Analyze residents "as randomized"; estimate the hazard ratio comparing the treatment groups with Cox proportional hazards regression with treatment as the only covariate.

[1]In the initial design of the study, we had considered examining stroke, intracerebral hemorrhage, and subarachnoid hemorrhage each as individual outcomes, but preliminary analyses of the study data demonstrated that there were too few users of each and reporting on them would have violated the Centers for Medicare & Medicaid Services Cell Size Suppression Policy governing our use of the data.

Supplementary Table S2. Covariates Included in the Propensity Score Estimation and Standardized Differences Before and After Propensity Score Matching.

	Original Value		Absolute Value	
Covariate Description	**Before Matching**	**After Matching**	**Before Matching**	**After Matching**
Bladder incontinence	0.11	0.07	0.11	0.07
Facility: % of other private pay clients	0.11	0.07	0.11	0.07
Bipolar disorder	0.02	0.06	0.02	0.06
Facility: Class of ownership (for-profit, non-profit, government)	0.05	0.06	0.05	0.06
Changes in Health, End-Stage Disease, and Signs and Symptoms Score (health instability)	0.06	0.06	0.06	0.06
Number of overnight hospitalizations	0.08	0.06	0.08	0.06
Facility: Staff hours per resident	0.09	0.06	0.09	0.06
Cognitive status (Cognitive Performance Scale score)	0.11	0.06	0.11	0.06
Number of emergency department visits	0.08	0.06	0.08	0.06
Antipsychotics	0.04	0.06	0.04	0.06
Pressure ulcers, presence, and stage	0.08	0.06	0.08	0.06
Intracranial hemorrhage hospitalization	0.05	0.06	0.05	0.06
Mood stabilizing or anticonvulsant	0.08	0.06	0.08	0.06
Aspirin or antiplatelet	-0.03	0.05	0.03	0.05
Change in ability to perform activities of daily living	0.03	0.05	0.03	0.05
Hearing performance	0.03	0.05	0.03	0.05
Social engagement	0.10	0.05	0.10	0.05
Resisted taking medications, activities of daily living assistance, or eating	0.04	0.05	0.04	0.05
Long-acting opioids	0.04	0.05	0.04	0.05
Intracranial hemorrhage emergency department visit	0.02	0.04	0.02	0.04
Problem behaviors present	-0.03	0.04	0.03	0.04
Cognitive ability varies over time	0.09	0.04	0.09	0.04
Bowel incontinence	0.09	0.04	0.09	0.04
Race/ethnicity	0.10	0.04	0.10	0.04
Transitions in care setting	0.13	0.04	0.13	0.04
Communication scale	0.10	0.04	0.10	0.04
Educational Attainment	0.07	0.04	0.07	0.04
Vision performance	0.09	0.04	0.09	0.04
Tramadol	0.05	0.03	0.05	0.03
Participation of medical director and/or other physician	0.06	0.03	0.06	0.03
Long-acting morphine	0.04	0.03	0.04	0.03

Reduced social interaction	0.01	0.03	0.01	0.03
Calendar year of sulfonylurea or dipeptidyl peptidase-4 inhibitor initiation	0.15	0.03	0.15	0.03
Facility: pharmacist full time equivalents	-0.02	0.03	0.02	0.03
Family participation in resident's care	0.05	0.03	0.05	0.03
Age	0.12	0.03	0.12	0.03
Pain presence and severity	0.07	0.03	0.07	0.03
Hip fracture emergency department visit	0.00	0.03	0.00	0.03
Peripheral vascular disease	0.03	0.02	0.03	0.02
Antibiotic resistant infection	0.01	0.02	0.01	0.02
Behavior status change	0.09	0.02	0.09	0.02
Hyperglycemia emergency department visit	0.10	0.02	0.10	0.02
Hyperthyroidism	0.03	0.02	0.03	0.02
Dehydration/fluid status care plan implemented	0.07	0.02	0.07	0.02
Body mass index	0.14	0.02	0.14	0.02
Intermediate-acting insulin months 6-12 (i.e., more than 6 months) before initiation	0.06	0.02	0.06	0.02
Acute myocardial infarction emergency department visits	-0.01	0.02	0.01	0.02
Facility: Percentage of residents receiving respiratory care	0.04	0.02	0.04	0.02
Antiarrhythmics	-0.01	0.02	0.01	0.02
Altered consciousness hospitalization	0.03	0.02	0.03	0.02
Diabetes mellitus	0.12	0.02	0.12	0.02
Complains about the taste of many foods	0.06	0.02	0.06	0.02
Short-acting insulin months 6-12 (i.e., more than 6 months) before initiation	0.14	0.02	0.14	0.02
Repetitive health complaints presence and frequency	0.03	0.02	0.03	0.02
Primary language spoken	0.05	0.02	0.05	0.02
Ostomy (bowel)	-0.05	0.02	0.05	0.02
Oral steroids	0.01	0.02	0.01	0.02
Customary routine includes alcoholic beverages at least weekly	0.00	0.02	0.00	0.02
Bisphosphonates	-0.01	0.02	0.01	0.02
Do not hospitalize advanced directive documented in the medical record	-0.06	0.02	0.06	0.02
Facility: Percentage of residents receiving psychoactive drugs	-0.01	0.02	0.01	0.02
Female sex	-0.02	0.02	0.02	0.02
Ventilator or respirator	0.03	0.01	0.03	0.01
Feeding restrictions advanced directive documented in the medical record	-0.05	0.01	0.05	0.01
Altered consciousness emergency department visit	0.02	0.01	0.02	0.01

Number of medications	0.25	0.01	0.25	0.01
Duration of nursing home stay before sulfonylurea or dipeptidyl peptidase-4 inhibitor initiation	0.04	0.01	0.04	0.01
Eating performance	0.05	0.01	0.05	0.01
Alpha blockers	-0.04	0.01	0.04	0.01
Gabapentin or pregabalin	0.08	0.01	0.08	0.01
Change in ability to express, understand, or hear information	0.04	0.01	0.04	0.01
Family member responsible for resident	0.00	0.01	0.00	0.01
Customary routine includes use of tobacco at least daily	-0.02	0.01	0.02	0.01
Therapeutic diet	-0.02	0.01	0.02	0.01
Clostridium difficile infection	0.03	0.01	0.03	0.01
Facility: Percentage of residents on a pharmacy pain management program	-0.03	0.01	0.03	0.01
Foot infection	0.02	0.01	0.02	0.01
Weight gain or loss of 3 or more pounds	-0.04	0.01	0.04	0.01
Facility: Percentage of residents with bedsores	0.06	0.01	0.06	0.01
Calcitonin	-0.03	0.01	0.03	0.01
Deep vein thrombosis	0.00	0.01	0.00	0.01
Dehydration/fluid status resident assessment triggered	0.06	0.01	0.06	0.01
Hearing aid present and used	-0.02	0.00	0.02	0.00
Statins	0.12	0.00	0.12	0.00
Cataracts	0.01	0.00	0.01	0.00
Edema	-0.01	0.00	0.01	0.00
Pathological bone fracture	-0.02	0.00	0.02	0.00
Hip fracture hospitalizations	0.02	0.00	0.02	0.00
Dizziness/vertigo	-0.01	0.00	0.01	0.00
Alpha-glucosidase inhibitors months 6-12 (i.e., more than 6 months) before initiation	0.05	0.00	0.05	0.00
Calcium channel blockers	0.03	0.00	0.03	0.00
Fibrates	0.11	0.00	0.11	0.00
Number of new medications	0.05	0.00	0.05	0.00
Long-acting insulin months 6-12 (i.e., more than 6 months) before initiation	0.24	0.00	0.24	0.00
Established own goals	-0.02	0.00	0.02	0.00
On a planned weight change program	0.04	0.00	0.04	0.00
Facility: Percentage of residents receiving antidepressants	-0.05	0.00	0.05	0.00
Potassium-sparing diuretics	0.08	0.00	0.08	0.00
Macular degeneration	0.00	0.00	0.00	0.00
Skin tears or cuts (other than surgery)	-0.04	0.00	0.04	0.00

Emphysema/chronic obstructive pulmonary disease	0.03	0.00	0.03	0.00
Ezetimibe	0.06	-0.01	0.06	0.01
Glasses, contact lenses, or magnifying glass used	-0.05	-0.01	0.05	0.01
Hip fracture	-0.01	-0.01	0.01	0.01
Abnormal laboratory values	0.10	-0.01	0.10	0.01
Hyperglycemia hospitalizations	0.09	-0.01	0.09	0.01
Raloxifene	0.01	-0.01	0.01	0.01
Heart failure emergency department visit	0.09	-0.01	0.09	0.01
Nonbenzodiazepine hypnotics	0.08	-0.01	0.08	0.01
Respiratory infection	0.00	-0.01	0.00	0.01
Received preventative or protective foot care	0.02	-0.01	0.02	0.01
Chewing problems	-0.02	-0.01	0.02	0.01
Bile acid sequestrants	0.02	-0.01	0.02	0.01
Angiotensin receptor blockers	0.11	-0.01	0.11	0.01
Aphasia	-0.03	-0.01	0.03	0.01
Facility: registered nurse full time equivalents per 100 beds	0.03	-0.01	0.03	0.01
Evaluation by a licensed mental specialist	0.04	-0.01	0.04	0.01
Diabetic retinopathy	-0.01	-0.01	0.01	0.01
Heart failure hospitalizations	0.12	-0.01	0.12	0.01
Facility: physical therapy full time equivalents per 100 beds	-0.03	-0.02	0.03	0.02
Dialysis	0.02	-0.02	0.02	0.02
Prefers exercise or sports	-0.02	-0.02	0.02	0.02
Do not resuscitate advanced directive documented in the medical record	-0.12	-0.02	0.12	0.02
Facility: medication error rate	-0.02	-0.02	0.02	0.02
Renal failure	0.03	-0.02	0.03	0.02
Alzheimer’s disease	-0.03	-0.02	0.03	0.02
Facility: acuity of residents (acuity index)	0.05	-0.02	0.05	0.02
Urinary tract infection	0.06	-0.02	0.06	0.02
Acute myocardial infarction hospitalizations	0.01	-0.02	0.01	0.02
Thiazide diuretics	0.06	-0.02	0.06	0.02
Hypoglycemia emergency department visit	0.10	-0.02	0.10	0.02
Depression	0.00	-0.02	0.00	0.02
Niacin medication	0.03	-0.02	0.03	0.02
Metformin	0.17	-0.02	0.17	0.02
Warfarin	0.03	-0.02	0.03	0.02
Glucagon	0.10	-0.02	0.10	0.02
Hearing aid present and not used regularly	-0.06	-0.02	0.06	0.02

Facility: Percentage of residents receiving antianxiety medications	0.02	-0.02	0.02	0.02
Omega-3 fatty acid medication	0.08	-0.02	0.08	0.02
Facility: Percentage of residents covered by Medicaid insurance	0.06	-0.02	0.06	0.02
Antidepressant medications	0.08	-0.02	0.08	0.02
Miscellaneous antihypertensive medications	0.06	-0.02	0.06	0.02
Anxiety disorder	-0.01	-0.02	0.01	0.02
Hypertension	-0.01	-0.02	0.01	0.02
Facility: nurse aide full time equivalents per 100 beds	-0.02	-0.02	0.02	0.02
Customary routine includes usual attendance at church, temple, synagogue, or other place of worship	-0.05	-0.02	0.05	0.02
Glaucoma	0.05	-0.02	0.05	0.02
Facility: count of quality-of-life deficiencies	0.03	-0.02	0.03	0.02
Stroke emergency department visits	0.04	-0.02	0.04	0.02
History of falls	-0.04	-0.02	0.04	0.02
Leaves 25% or more of food uneaten at most meals	-0.02	-0.02	0.02	0.02
Stroke	0.01	-0.03	0.01	0.03
Muscle relaxant medications	0.09	-0.03	0.09	0.03
Parenteral/intravenous feeding	0.05	-0.03	0.05	0.03
Angiotensin-converting enzyme inhibitors	0.09	-0.03	0.09	0.03
Customary routine includes daily contact with relatives or close friends	-0.05	-0.03	0.05	0.03
Hypoglycemia hospitalizations	0.11	-0.03	0.11	0.03
Seizure disorders	0.02	-0.03	0.02	0.03
Missing limb or amputation	-0.03	-0.03	0.03	0.03
Wound infection	0.05	-0.03	0.05	0.03
Thiazolidinediones months 6-12 (i.e., more than 6 months) before initiation	0.21	-0.03	0.21	0.03
Cardiac dysrhythmias	0.00	-0.03	0.00	0.03
Congestive heart failure	0.06	-0.03	0.06	0.03
Nutrition status care plan implemented	0.09	-0.03	0.09	0.03
Rapid-acting insulin months 6-12 (i.e., more than 6 months) before initiation	0.23	-0.03	0.23	0.03
Stroke hospitalization	0.03	-0.03	0.03	0.03
Weight loss of 5% or more in the last 30 days or 10% or more in the last 180 days	0.02	-0.04	0.02	0.04
Side vision problems or decreased peripheral vision	-0.02	-0.04	0.02	0.04
Any acute episode or a flare-up of a recurrent or chronic health problem	0.08	-0.04	0.08	0.04
Other cardiovascular disease	0.00	-0.04	0.00	0.04

Proton pump inhibitors	0.13	-0.04	0.13	0.04
Nutritional status resident assessment triggered	0.07	-0.04	0.07	0.04
Hallucinations	-0.02	-0.04	0.02	0.04
Some or all natural teeth were lost	0.04	-0.04	0.04	0.04
Beta blockers	0.11	-0.04	0.11	0.04
Facility: part of a nursing home chain	-0.03	-0.04	0.03	0.04
Dementia other than Alzheimer's disease	-0.04	-0.04	0.04	0.04
At ease doing self-initiated activities	-0.06	-0.04	0.06	0.04
Delirium resident assessment triggered	-0.07	-0.04	0.07	0.04
Morris activities of daily living scale (0-28 point)	0.00	-0.05	0.00	0.05
Anti-anxiety medication	0.02	-0.05	0.02	0.05
Osteoporosis	0.00	-0.05	0.00	0.05
Facility: Percentage of residents physically restrained	0.04	-0.05	0.04	0.05
Hypotension	-0.03	-0.05	0.03	0.05
Dietary supplement between meals	0.02	-0.05	0.02	0.05
Number of physician visits	0.04	-0.05	0.04	0.05
Hypothyroidism	0.02	-0.05	0.02	0.05
Number of orders changed by physician	0.11	-0.05	0.11	0.05
Arthritis	0.01	-0.05	0.01	0.05
Clopidogrel	0.15	-0.05	0.15	0.05
Facility: Off-site pharmacy	0.04	-0.05	0.04	0.05
Facility: Organized family group	0.04	-0.05	0.04	0.05
Mechanically altered diet	-0.01	-0.05	0.01	0.05
Anemia	0.04	-0.05	0.04	0.05
Any intravenous medications	0.05	-0.06	0.05	0.06
Nutrition or hydration intervention to manage skin problems	0.06	-0.06	0.06	0.06
Arteriosclerotic heart disease	0.07	-0.06	0.07	0.06
Number of comorbidities	0.05	-0.06	0.05	0.06

Supplementary Table S3. Effects of Dipeptidyl Peptidase-4 Inhibitors versus Sulfonylureas on Mortality, Adverse Glycemic, and Adverse Cardiovascular Outcomes Using Multiple Imputation of Missing Pretreatment Covariate Information.

		Hazard Ratio (95% Confidence Interval)	
Outcome	**Follow-up**	**Unmatched**	**Matched**
Hypoglycemia	180 days	0.97 (0.58-1.64)	0.75 (0.37-1.49)
	365 days	0.78 (0.51-1.17)	0.60 (0.36-1.00)
Hyperglycemia	365 days	1.17 (0.78-1.75)	0.90 (0.52-1.57)
Acute Myocardial Infarction	180 days	1.14 (0.64-2.03)	1.05 (0.40-2.79)
	365 days	0.97 (0.63-1.50)	0.96 (0.49-1.87)
Heart Failure	90 days	1.39 (1.02-1.89)	1.35 (0.70-2.62)
	180 days	1.37 (1.08-1.73)	1.29 (0.85-1.98)
	365 days	1.25 (1.04-1.49)	1.17 (0.87-1.57)
Major Adverse Cardiovascular Events + Heart Failure	90 days	1.33 (0.99-1.78)	1.21 (0.71-2.07)
	180 days	1.27 (1.02-1.58)	1.17 (0.81-1.70)
	365 days	1.16 (0.98-1.37)	1.08 (0.82-1.42)
All-cause Mortality	90 days	1.14 (0.96-1.35)	1.11 (0.86-1.43)
	180 days	1.12 (0.99-1.27)	1.06 (0.86-1.30)
	365 days	1.08 (0.99-1.19)	0.98 (0.86-1.13)

Note 1: We were concerned about the sample size reduction due to missing pretreatment covariate information. We were also concerned that pretreatment covariate information might be missing for a reason related to the outcomes we studied. Therefore, we used multiple imputation to impute the missing information for covariates that were used to estimate the propensity score. No outcome information was imputed. We assumed that the covariate information was missing at random. We used the fully conditional specification method (i.e., iterative chained equations) with the discriminant function and logistic regression to impute the missing values because many covariates must only take on specific discrete values. We multiply imputed 10 datasets. No auxiliary covariates were included in the imputation model, but all covariates used in the propensity score estimation model were included. Covariate information was missing for 111 covariates. The covariates with the greatest proportion of missing values were the number of quality-of-life deficiencies in the nursing home (n=213, 2.5%), the highest educational level attained by the resident (n=171, 2.0%), whether care was needed for fluid maintenance or dehydration (n=153, 1.8%), and the primary language used by the resident (n=101, 1.2%). All but 11 covariates had a proportion of values missing that was ≤0.005 (0.5% missing). To obtain the propensity score-matched estimates, we followed our primary analytic approach and performed the propensity score estimation and matching in each multiply imputed complete dataset. We then estimated the outcome model in each imputed dataset, and pooled the parameter estimates across the datasets using the formulas previously developed by Rubin.

Note 2: In the initial design of the study, we had planned to examine 90-day hypoglycemia, 90-day hyperglycemia, 90-day acute myocardial infarction, and 180-day hyperglycemia outcomes, but preliminary analyses of the study data demonstrated that there were too few outcome events and reporting on them would have violated the Centers for Medicare & Medicaid Services Cell Size Suppression Policy governing our use of the data.

Supplementary Table S4. Effects of Dipeptidyl Peptidase-4 Inhibitors versus Sulfonylureas on Mortality, Adverse Glycemic, and Adverse Cardiovascular Outcomes at 3 months and 6 months.

			Unmatched				Matched			
Follow-up Period	**Outcome**	**Treatment**	**Events**	**Person-Years**	**Rate***	**HR (95% CI)**	**Events**	**Person-Years**	**Rate***	**HR (95% CI)**
90 days	Hypoglycemia	DPP4I	<11	NA	NA	NA	<11	NA	NA	NA
		SU	54	1,540.9	35.0	NA	<11	NA	NA	NA
	Hyperglycemia	DPP4I	<11	NA	NA	NA	<11	NA	NA	NA
		SU	36	1,542.5	23.3	NA	<11	NA	NA	NA
	Acute Myocardial Infarction	DPP4I	<11	NA	NA	NA	<11	NA	NA	NA
		SU	48	1,542.3	31.1	NA	<11	NA	NA	NA
	Heart Failure	DPP4I	44	230.7	190.7	1.30 (0.94-1.79)	43	227.7	188.9	1.32 (0.84-2.07)
		SU	225	1,528.1	147.2	Ref	33	230.7	143.0	Ref
	Major Adverse Cardiovascular Events + Heart Failure	DPP4I	50	236.4	211.5	1.25 (0.93-1.70)	49	227.3	215.6	1.18 (0.79-1.77)
		SU	264	1,541.7	171.2	Ref	42	230.2	182.5	Ref
	All-cause Mortality	DPP4I	159	244.1	651.4	1.17 (0.99-1.39)	147	231.4	635.3	1.12 (0.88-1.41)
		SU	875	1,571.5	556.8	Ref	133	233.1	570.6	Ref
180 days	Hypoglycemia	DPP4I	16	432.6	37.0	1.01 (0.60-1.72)	15	427.2	35.1	0.79 (0.41-1.54)
		SU	105	2,877.0	36.5	Ref	19	429.2	44.3	Ref
	Hyperglycemia	DPP4I	<11	NA	NA	NA	<11	NA	NA	NA
		SU	76	2,881.7	26.4	NA	<11	NA	NA	NA
	Acute Myocardial Infarction	DPP4I	13	433.9	30.0	1.14 (0.63-2.05)	13	428.4	30.4	0.94 (0.44-1.99)
		SU	76	2,884.5	26.3	Ref	14	430.6	32.5	Ref
	Heart Failure	DPP4I	78	424.9	183.6	1.31 (1.02-1.66)	77	419.7	183.5	1.26 (0.90-1.76)
		SU	399	2,839.1	140.5	Ref	62	424.9	145.9	Ref
	Major Adverse Cardiovascular Events + Heart Failure	DPP4I	87	428.5	203.0	1.23 (0.98-1.54)	85	423.2	200.9	1.13 (0.83-1.54)
		SU	473	2,841.8	166.4	Ref	76	423.3	179.5	Ref
	All-cause Mortality	DPP4I	290	451.4	642.5	1.15 (1.02-1.31)	266	429.2	619.8	1.00 (0.84-1.19)
		SU	1,640	2,941.7	557.5	Ref	268	432.0	620.4	Ref

*Per 1,000 person-years of follow-up.

Note: In the initial design of the study, we had planned to examine 90-day hypoglycemia, 90-day hyperglycemia, 90-day acute myocardial infarction, and 180-day hyperglycemia outcomes, but preliminary analyses of the study data demonstrated that there were too few outcome events and reporting on them would have violated the Centers for Medicare & Medicaid Services Cell Size Suppression Policy governing our use of the data.

Supplementary Table S5. Effects of Dipeptidyl Peptidase-4 Inhibitors versus Sulfonylureas on Mortality, Adverse Glycemic, and Adverse Cardiovascular Outcomes Using Generalized Boosted Regression to Estimate the Propensity Score (N=1,790).

Outcome	Follow-up	Hazard Ratio (95% Confidence Interval)
Hypoglycemia	180 days	0.98 (0.48-2.00)
	365 days	0.57 (0.34-0.97)
Hyperglycemia	365 days	0.65 (0.37-1.14)
Acute Myocardial Infarction	180 days	0.75 (0.33-1.72)
	365 days	0.58 (0.32-1.04)
Heart Failure	90 days	0.92 (0.59-1.44)
	180 days	0.89 (0.64-1.25)
	365 days	0.80 (0.62-1.03)
Major Adverse Cardiovascular Events + Heart Failure	90 days	0.97 (0.63-1.48)
	180 days	0.89 (0.65-1.22)
	365 days	0.81 (0.64-1.02)
All-cause Mortality	90 days	0.89 (0.70-1.13)
	180 days	0.83 (0.70-0.99)
	365 days	0.83 (0.73-0.95)

Note 1: Since misspecification of the propensity score estimation model is a possibility that can influence the results of our study, we employed generalized boosted regression as an alternative propensity score estimation approach. There were 895 new SU users matched to 895 new DPP4I users. The distribution of propensity scores was nearly identical between the matched groups (P=0.82 for the difference in the mean propensity scores between the treatment groups); the mean (SD) was 0.19 (0.07) in both the SU and DPP4I users.

Note 2: In the initial design of the study, we had planned to examine 90-day hypoglycemia, 90-day hyperglycemia, 90-day acute myocardial infarction, and 180-day hyperglycemia outcomes, but preliminary analyses of the study data demonstrated that there were too few outcome events and reporting on them would have violated the Centers for Medicare & Medicaid Services Cell Size Suppression Policy governing our use of the data.

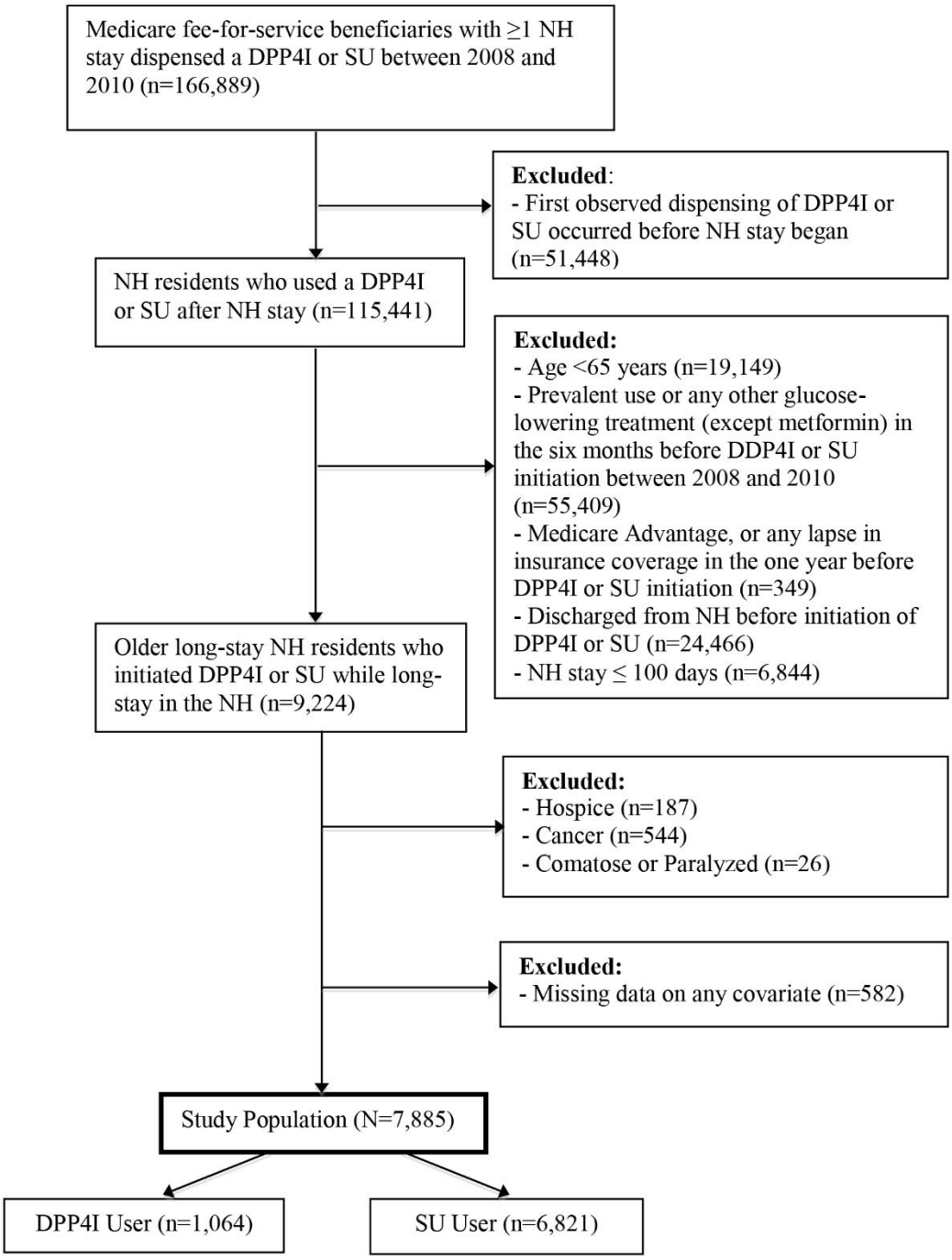
Supplementary Table S6. Effects of Dipeptidyl Peptidase-4 Inhibitors versus Sulfonylureas on Adverse Glycemic and Cardiovascular Outcomes Using Fine and Gray Models to Address the Competing Risk of Death.

		Hazard Ratio (95% Confidence Interval)	
Outcome	**Follow-up**	**Unmatched**	**Matched**
Hypoglycemia	180 days	1.00 (0.57-1.64)	0.79 (0.39-1.55)
	365 days	0.76 (0.49-1.14)	0.57 (0.34-0.95)
Hyperglycemia	365 days	0.97 (0.60-1.50)	0.96 (0.52-1.74)
Acute Myocardial Infarction	180 days	1.13 (0.60-1.96)	0.93 (0.43-1.99)
	365 days	0.98 (0.61-1.48)	0.77 (0.44-1.31)
Heart Failure	90 days	1.30 (0.93-1.77)	1.31 (0.84-2.08)
	180 days	1.30 (1.01-1.64)	1.25 (0.90-1.75)
	365 days	1.20 (1.00-1.44)	1.03 (0.81-1.32)
Major Adverse Cardiovascular Events + Heart Failure	90 days	1.26 (0.92-1.69)	1.17 (0.78-1.78)
	180 days	1.23 (0.97-1.53)	1.13 (0.83-1.54)
	365 days	1.14 (0.95-1.35)	0.91 (0.73-1.15)

Note 1: Death is common in the nursing home setting and can preclude the observation of other events like adverse glycemic and cardiovascular outcomes. This creates two potential problems when using the Cox proportional hazards regression model. First, the independent censoring assumption that the future risk of those whose follow-up has ended can be represented by nursing home residents who are followed longer becomes suspect. Such an assumption may be too strong for frail older individuals in the nursing home setting. Second, the Cox proportional hazards regression models attempt to project forward the experience of a censored nursing home resident by representing their experience with those residents who were followed longer. To extrapolate to a setting where death is not possible would be to project to a new population or the ability to extend lives, which alters the underlying conditions of the study. Therefore, we can acknowledge death as another possible outcome and end follow-up for other outcomes rather than attempt to project experience beyond nursing home residents' lifetimes. Since exposure to dipeptidyl peptidase-4 inhibitors versus sulfonylureas might be related to unmeasured confounding covariates that increase the risk of death, we were interested in examining outcomes on the cumulative incidence scale. To do so, we employed Fine and Gray regressions. These regressions adapt the essence of the Cox proportional hazards model to the cumulative incidence formulation by modeling a different kind of rate function. The Fine and Gray approach counts nursing home residents who die in the denominator of the rate. In doing so, the model acknowledges that individuals who succumb to a competing risk (like death) will not develop the event of interest and more importantly, does not require extrapolation to a setting where death is not possible.

Note 2: In the initial design of the study, we had planned to examine 90-day hypoglycemia, 90-day hyperglycemia, 90-day acute myocardial infarction, and 180-day hyperglycemia outcomes, but preliminary analyses of the study data demonstrated that there were too few outcome events and reporting on them would have violated the Centers for Medicare & Medicaid Services Cell Size Suppression Policy governing our use of the data.

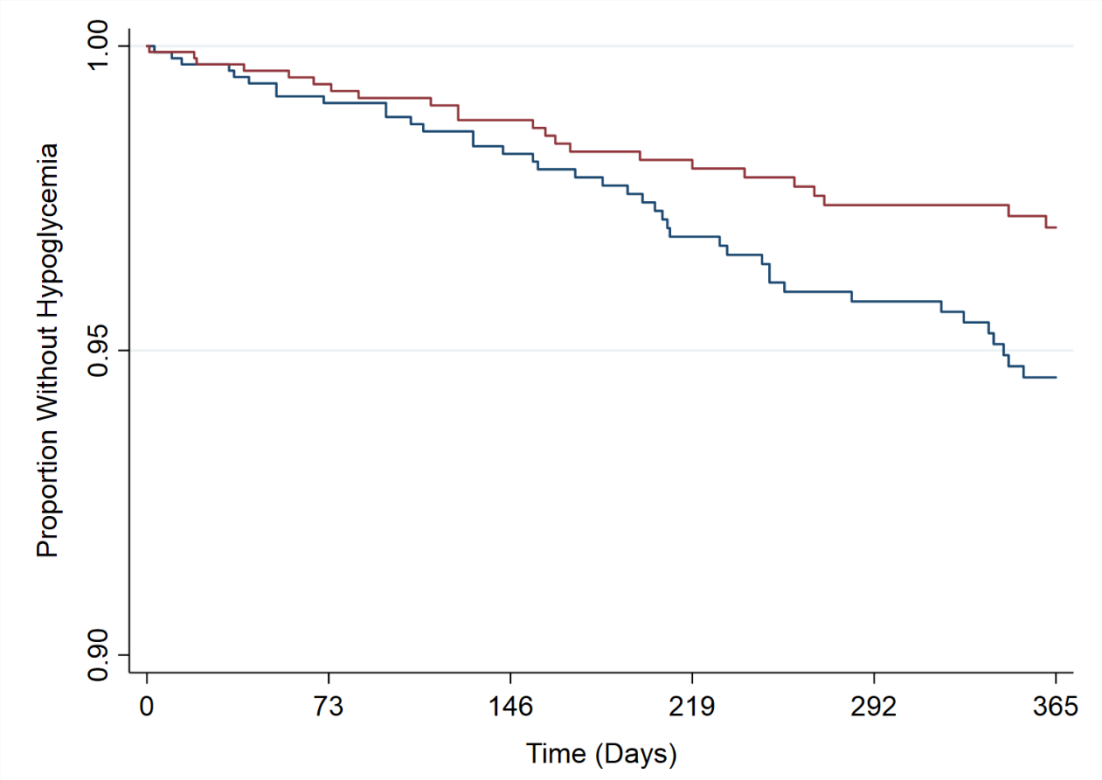
Supplementary Figure S1. Study Cohort Flow Diagram.



Note: We identified 166,889 Medicare beneficiaries with at least one nursing home stay and a dispensing of a DPP4I or SU between 2008 and 2010. We excluded prior recipients of a DPP4I or SU (n=51,448) and individuals who were <65 years old (n=19,149). We also excluded recipients of a glucose-lowering treatment other than metformin within six months of initiation (n=55,409) with the aim of reducing confounding by prior glucose-lowering treatment. Use of prior glucose-lowering treatments is a high-

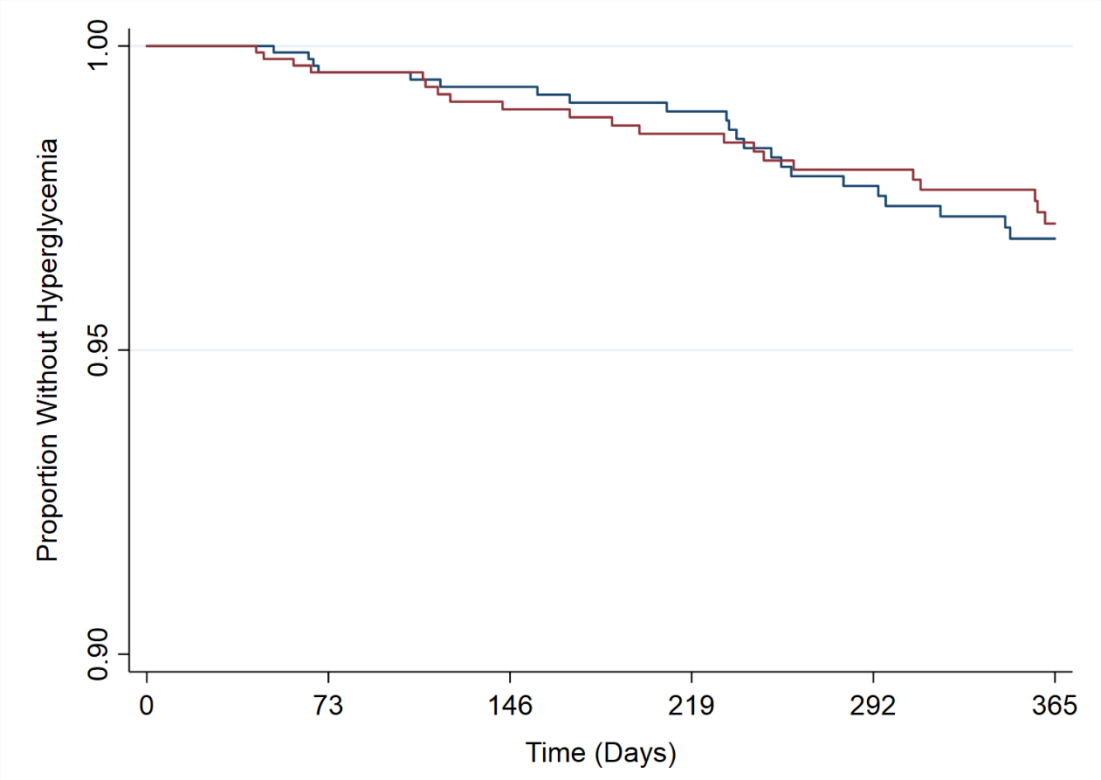
dimensional space consisting of numerous treatment combinations because nursing home residents are often treated in ways that inexplicably deviate from clinical guidelines (for empirical confirmation, please see Zullo AR, Dore DD, Gutman R, Mor V, Smith RJ. National Glucose-Lowering Treatment Complexity Is Greater in Nursing Home Residents than Community- Dwelling Adults. J Am Geriatr Soc. 2016 Nov;64(11):e233-e235. doi: 10.1111/jgs.14485. Epub 2016 Sep 27. PMID: 27677102).

Supplementary Figure S2. Kaplan Meier Plot of Hypoglycemia over 365 Days of Follow-Up Stratified by Dipeptidyl Peptidase-4 inhibitor Versus Sulfonylurea Use after Propensity Score Matching.



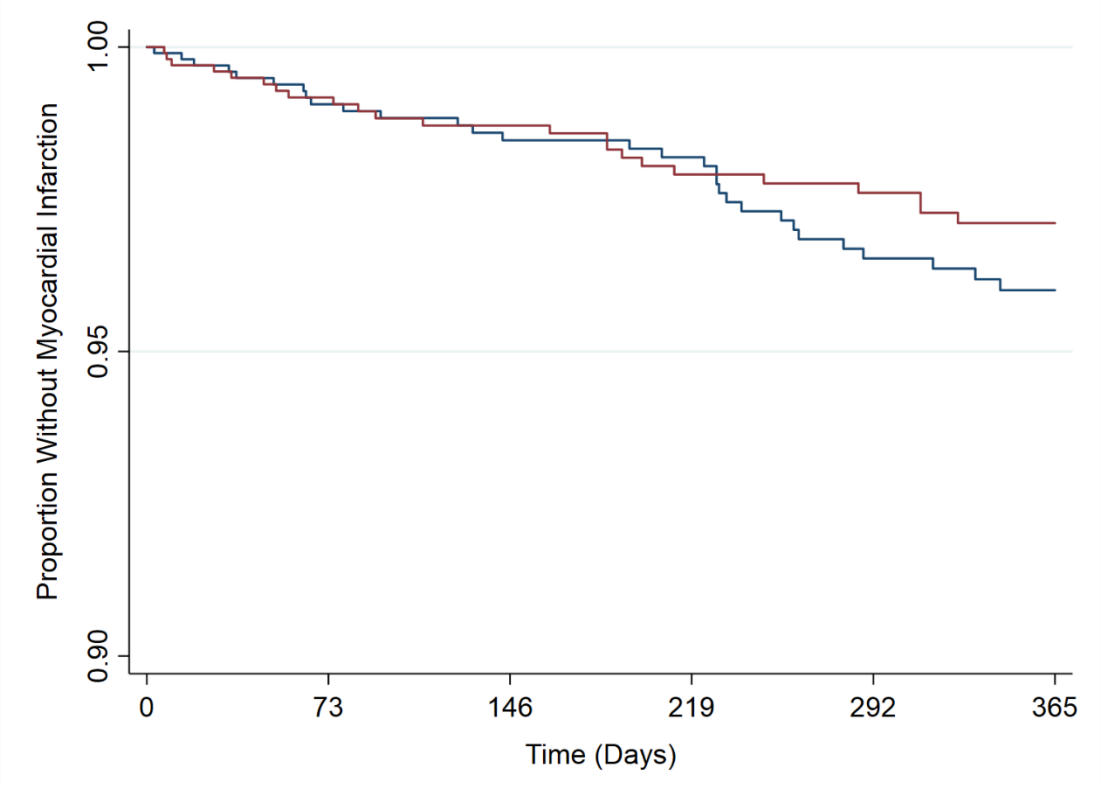
Note: DPP4I users are represented by the red line. SU users are represented by the blue lines. Lines are survival curves.

Supplementary Figure S3. Kaplan Meier Plot of Hyperglycemia over 365 Days of Follow-Up Stratified by Dipeptidyl Peptidase-4 inhibitor Versus Sulfonylurea Use after Propensity Score Matching.



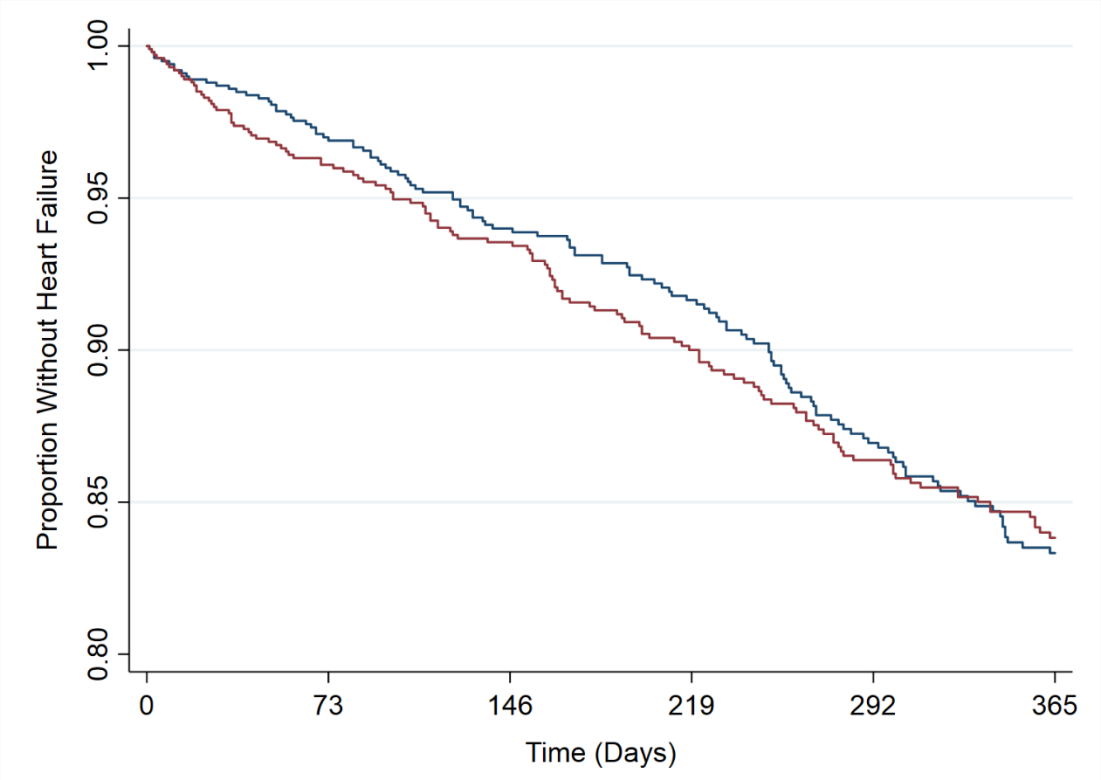
Note: DPP4I users are represented by the red line. SU users are represented by the blue lines. Lines are survival curves.

Supplementary Figure S4. Kaplan Meier Plot of Acute Myocardial Infarction over 365 Days of Follow-Up Stratified by Dipeptidyl Peptidase-4 inhibitor Versus Sulfonylurea Use after Propensity Score Matching.



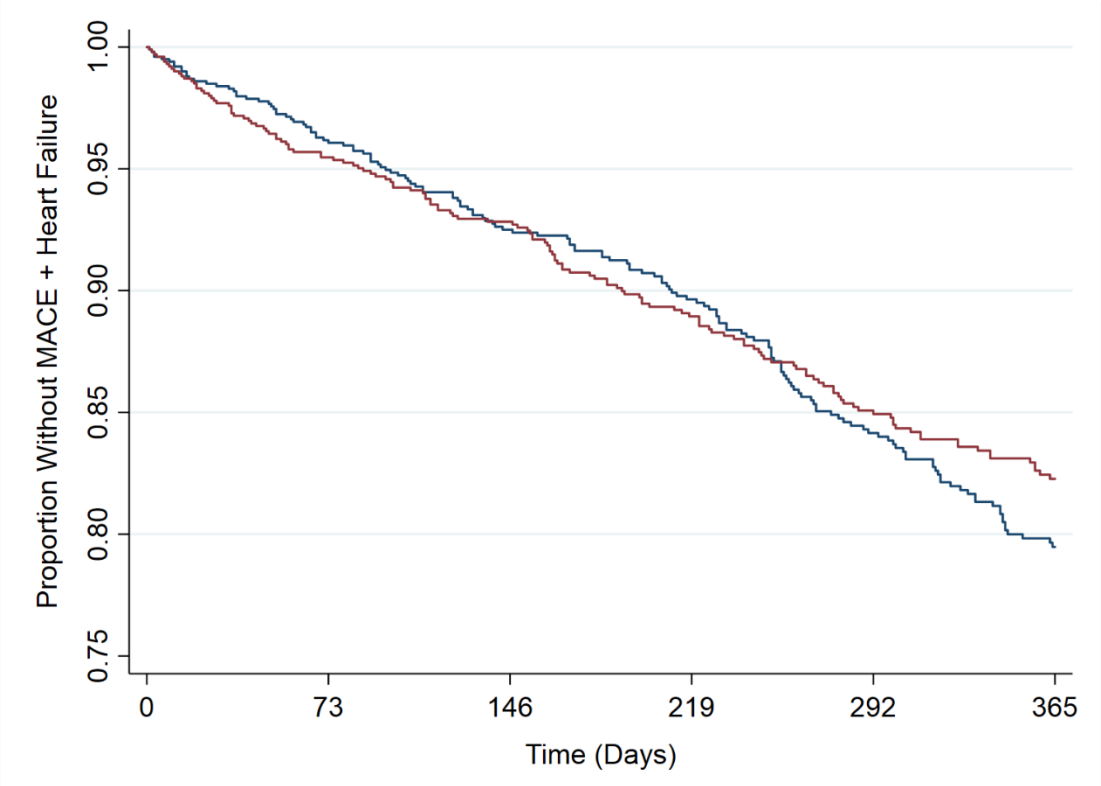
Note: DPP4I users are represented by the red line. SU users are represented by the blue lines. Lines are survival curves.

Supplementary Figure S5. Kaplan Meier Plot of Heart Failure over 365 Days of Follow-Up Stratified by Dipeptidyl Peptidase-4 inhibitor Versus Sulfonylurea Use after Propensity Score Matching.



Note: DPP4I users are represented by the red line. SU users are represented by the blue lines. Lines are survival curves.

Supplementary Figure S6. Kaplan Meier Plot of Major Adverse Cardiovascular Events plus Heart Failure over 365 Days of Follow-Up Stratified by Dipeptidyl Peptidase-4 inhibitor Versus Sulfonylurea Use after Propensity Score Matching.



Note: DPP4I users are represented by the red line. SU users are represented by the blue lines. Lines are survival curves.

Supplementary Methods 1. Measurement of outcomes.

Adverse glycemic events included hypoglycemia (ICD-9-CM codes 251.0X, 251.1X, or 251.2X; algorithm positive predictive value [PPV], 89%) and hyperglycemia (ICD-9-CM codes 250.02, 250.03, 250.1, 250.2, 250.3; PPV unavailable).[1] The MACE events included acute myocardial infarction (ICD-9-CM code 410.X; PPV, 67-97%)[2-4], stroke (including ischemic stroke [ICD-9-CM codes 433.X1, 434.X excluding 434.X0, or 436], intracerebral hemorrhage [ICD-9-CM code 431], and subarachnoid hemorrhage [ICD-9-CM code 430], but excluding traumatic brain injury [ICD-9-CM codes 800 to 804 and 850 to 854]; PPV, 97%)[5], and heart failure (402.X1, 404.X1, 404.X3, or 428.X; PPV, 90%)[6].

Supplementary Methods 1 References

1. Ginde AA, Blanc PG, Lieberman RM, Camargo CA, Jr. Validation of ICD-9-CM coding algorithm for improved identification of hypoglycemia visits. BMC endocrine disorders. 2008;8:4.
2. Choma NN, Griffin MR, Huang RL, et al. An algorithm to identify incident myocardial infarction using Medicaid data. Pharmacoepidemiology and drug safety. 2009;18(11):1064-1071.
3. Rosamond WD, Chambless LE, Sorlie PD, et al. Trends in the sensitivity, positive predictive value, false-positive rate, and comparability ratio of hospital discharge diagnosis codes for acute myocardial infarction in four US communities, 1987-2000. American journal of epidemiology. 2004;160(12):1137-1146.
4. Petersen LA, Wright S, Normand SL, Daley J. Positive predictive value of the diagnosis of acute myocardial infarction in an administrative database. Journal of general internal medicine. 1999;14(9):555-558.
5. Roumie CL, Mitchel E, Gideon PS, Varas-Lorenzo C, Castellsague J, Griffin MR. Validation of ICD-9 codes with a high positive predictive value for incident strokes resulting in hospitalization using Medicaid health data. Pharmacoepidemiology and drug safety. 2008;17(1):20-26.

6. Saczynski JS, Andrade SE, Harrold LR, et al. A systematic review of validated methods for identifying heart failure using administrative data. Pharmacoepidemiology and drug safety. 2012;21 Suppl 1:129-140.

Supplementary Methods 2. Sensitivity analysis using the E-value.

To assess how robust our findings were to potential unmeasured or residual confounding, we conducted a sensitivity analysis using the E-value (VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. Annals of internal medicine. 2017;167(4):268-274.). The E-value is the minimum strength of association, on the risk ratio scale, that an unmeasured confounder would need to have with both DPP4I versus SU use and an outcome to fully explain away the observed treatment effect estimate (i.e., if there truly was no effect). E-values may be used to assess, for example, how strong the relationship must be between hemoglobin A1c (a potential unmeasured confounder) and the decision to prescribe DPP4Is instead of SUs (the exposure) and having a hypoglycemia event (an outcome) to fully explain the observed findings. Larger E-values suggest that the results are more robust to residual confounding because the unmeasured confounder must have a stronger association with both the treatment and outcome to explain the findings. We calculated E-values for the main 1-year hypoglycemia estimates, which were the only estimates that were statistically significant at the alpha=0.05 significance level.