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Comparative Safety of Dipeptidyl Peptidase-4 Inhibitors and Sulfonylureas among Frail Older Adults

Andrew R. Zullo, PharmD, PhD[1,2,3,4], **Robert J. Smith, MD**[1,5], **Roee Gutman, PhD**[6], **Bianca Kohler, PharmD**[4], **Matthew S. Duprey, PharmD, PhD**[1], **Sarah D. Berry, MD, MPH**[7,8], **Medha N. Munshi, MD**[8,9], **David D. Dore, PharmD, PhD**[1,10]

[1]Department of Health Services, Policy, and Practice, Brown University School of Public Health, Providence, RI

[2]Department of Epidemiology, Brown University School of Public Health, Providence, Rhode Island

[3]Center of Innovation in Long-Term Services and Supports, Providence Veterans Affairs Medical Center, Providence, RI

[4]Department of Pharmacy, Lifespan—Rhode Island Hospital, Providence, RI

[5]Warren Alpert Medical School, Brown University, Providence, RI

[6]Department of Biostatistics, Brown University School of Public Health, Providence, RI

[7]Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA

[8]Marcus Institute for Aging Research, Hebrew SeniorLife, Boston, MA

[9]Joslin Diabetes Center, Boston, MA

[10]Center for Health Sciences, Exponent, Inc., Natick, MA

Abstract

Correspondence: Andrew R. Zullo, PharmD, PhD, Department of Health Services, Policy, and Practice, Brown University School of Public Health, 121 South Main Street, Box G-S121-8, Providence, RI, 02912, Phone: 401-863-6309, andrew_zullo@brown.edu.

Author Contributions:

1. Conception and design: ARZ, RJS, RG, DDD.
2. Acquisition of data: ARZ, DDD.
3. Analysis of data: ARZ, RG.
4. Interpretation of data: All authors.
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Background: Studies comparing dipeptidyl peptidase-4 inhibitors (DPP4Is) to sulfonylureas (SUs) are unavailable for frail older adults, especially nursing home (NH) residents. We examined the effects of DPP4Is versus SUs on severe adverse glycemic events, cardiovascular events, and death among NH residents.

Methods: We conducted a national retrospective cohort study of long-stay NH residents aged ≥ 65 years using 2008 to 2010 national US Minimum Data Set clinical assessment data and linked Medicare claims. Exposure was new DPP4I versus new SU use assessed via Medicare Part D drug claims. One-year outcomes were severe hypoglycemia, severe hyperglycemia, acute myocardial infarction (AMI), heart failure (HF), major adverse cardiovascular events plus HF (MACE+HF), and death. We compared outcomes after propensity score matching using Cox proportional hazards regression models.

Results: The cohort (N=2,016) had a mean (SD) age of 81 (8.1) years and was 72% female. Compared to SU users, DPP4I users had a lower one-year rate of severe hypoglycemic events (HR=0.57, 95%CI 0.34-0.94), but statistically-similar rates of severe hyperglycemic events (HR=0.94, 95%CI 0.52-1.72), AMI (HR=0.76, 95%CI 0.44-1.30), HF (HR=1.01, 95%CI 0.79-1.30), MACE+HF (HR=0.90, 95%CI 0.72-1.12), and death (HR=0.97, 95%CI 0.86-1.10).

Conclusions: DPP4Is should be a preferred treatment option over SUs for NH residents and other frail older adults given the importance of avoiding hypoglycemia.

Keywords

Sulfonylurea Compounds; Dipeptidyl-Peptidase IV Inhibitors; Nursing Homes; Diabetes Mellitus; Frailty

INTRODUCTION

The prevalence of type 2 diabetes (T2DM) exceeds 30% in nursing home residents, yet little data exist to support the safest and most effective glucose-lowering treatment regimens. Avoiding hypoglycemia rather than achieving strict glycemic targets is generally the primary goal for most NH residents with T2DM.[1] While metformin remains the first-line recommended treatment for older adults with T2DM, it is infrequently used in nursing homes (NHs) given the high burden of chronic renal failure. In fact, as few as 6% of NH residents with T2DM use metformin monotherapy and just 30% use metformin with other glucose-lowering treatments.[2, 3] Sulfonylureas (SUs) are often used as monotherapy instead[2, 3], but are potentially harmful for NH residents given their high risk of hypoglycemia. Fortunately, several newer agents are available as alternatives to SUs, in particular, dipeptidyl peptidase-4 inhibitors (DPP4Is).

The use of DPP4Is has been increasing among NH residents in recent years, though little is known about the comparative safety and efficacy of DPP4Is and SUs in this unique population.[2, 3] Vulnerable older adults may be particularly susceptible to adverse effects of glucose-lowering medications and may also be less likely to live long enough to benefit from their preventative effects.[4] A large randomized controlled trial of community-dwelling adults with T2DM, the Cardiovascular Outcome Study of Linagliptin vs Glimepiride in Type 2 Diabetes (CAROLINA) trial, suggested no difference in efficacy of DDP4Is and SUs as

the investigators found similar rates of cardiovascular events among subjects randomized to glimepiride versus linagliptin.[5, 6] Overall rates of adverse events were similar between the two drug classes, but hypoglycemia was more common with SU than DDP4I use. However, the mean age of subjects in this trial was just 64 years with the vast majority (83%) concomitant metformin users. Thus, uncertainty remains as to the whether these drug classes are similarly effective and safe in a frail older population, such as NH residents. This knowledge gap, and the vulnerability of older NH residents, warrants a comparison of DPP4Is versus SUs.

We compared the effects of DPP4Is versus SUs on adverse glycemic events, adverse cardiovascular events, and death among frail, older adults in NHs. We hypothesized that prescribing DPP4Is would result in fewer severe hypoglycemic events, but no difference in other outcomes compared to SUs.

METHODS

Study Design and Data Source

This was a retrospective new-user cohort study that used the following linked national datasets for 2007-2010: Medicare fee-for-service enrollment information, Part A inpatient claims, Part B outpatient claims, and Part D prescription drug claims; Minimum Data Set (MDS) version 2.0 assessments; and Online Survey Certification and Reporting System (OSCAR) data. The MDS is a comprehensive, clinical assessment instrument used to document health status of NH residents, including functional status, cognitive status, and psychological information. OSCAR data provided NH-level information. Our observational study was designed to emulate a hypothetical pragmatic trial that could have been conducted had it been feasible (Table S1).[7, 8] This study was approved by the Brown University Institutional Review Board.

Study Population

The study population was adults aged ≥65 years who were long-stay NH residents (>100 days in the NH) on January 1, 2008, or who became a long-stay resident between January 1, 2008 and September 30, 2010. The index date was the date of the first eligible dispensing of a DPP4I or SU between January 1, 2008 and September 30, 2010 after becoming a long-stay resident. Individuals were required to have continuous enrollment in fee-for-service (i.e., traditional) Medicare Parts A, B, and D and no enrollment in Medicare Advantage in the twelve months prior to the index date. Individuals who were in hospice, had cancer, who were comatose or paralyzed, or who had missing data on any covariate used in the analyses were excluded from the study cohort (Supplementary Figure S1).

Exposures and Causal Contrast of Interest

Exposures of interest were new use of DPP4Is (saxagliptin, sitagliptin) or SUs (glimepiride, glipizide, glyburide) in the NH.[9] New use was defined as the first dispensing of a DPP4I or SU after 6 months without a dispensing of either class or another glucose-lowering treatment other than metformin. The causal contrasts of interest were defined as the effects of initiating

DPP4Is versus SUs regardless of subsequent treatment discontinuation or switching (i.e., the observational study analog of the intention-to-treat [ITT] estimand).[7, 8]

Outcomes

The outcomes were all-cause death, and hospitalizations or emergency department (ED) visits for adverse glycemic events (severe hypoglycemia and hyperglycemia), heart failure (HF), and major adverse cardiovascular events (MACE) plus HF. MACE included acute myocardial infarction (AMI), stroke, intracerebral hemorrhage, and subarachnoid hemorrhage. All of the non-death outcomes were defined using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes on Part A hospital claims and Part B ED claims in any coding position (Supplementary Methods 1).

Follow-Up

Follow-up started on the day after the first DPP4I or SU dispensing and continued until Medicare disenrollment (from Parts A, B, or D) or enrollment in Medicare Advantage, death, an outcome (each evaluated separately), one year of follow-up, or study end (December 31, 2010).

Baseline characteristics

One hundred ninety eight characteristics that were correlated with receiving DPP4Is versus SUs and the outcomes were pre-specified and measured before the index date (Supplementary Table S2).[2, 3, 10] The 198 characteristics that we selected *a priori* were all expected to be variables (or proxies of variables) that would either influence 1) both the probability of exposure to DPP4Is versus SUs and experiencing an outcome, or 2) just the probability of experiencing an outcome.[11]

Statistical Analyses

We adjusted for potential confounding by baseline covariates by estimating propensity scores using a logistic regression model that included the 198 baseline characteristics to predict the initiation of DPP4Is versus SUs. We matched DPP4I to SU users using a 1:1 greedy (nearest neighbor) 5-to-1 digit matching algorithm without replacement.[12] Cox proportional hazards regression models with robust standard errors were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) comparing DPP4I versus SU users.

Stability and Sensitivity Analyses

We conducted several stability analyses to test the robustness of the treatment effect estimates to study design and analytic decisions. First, to assess the impact of missing data, we performed multiple imputation with chained equations to impute missing covariate data for 582 residents excluded from the primary analysis.[13] Second, because the risk for misclassification of treatment is higher over longer follow-up periods with the ITT estimand, we examined 3-month and 6-month outcomes. Third, we estimated the propensity score using generalized boosted regression models to evaluate possible misspecification of the parametric propensity score model. Fourth, we used Fine and Gray competing

risks regression models to account for the potential competing risk of death. Finally, we conducted a sensitivity analysis using the E-value (see Supplementary Methods 2).[14]

RESULTS

Study Cohort

The study cohort (N=7,885) included 1,064 new DPP4I and 6,821 new SU users before propensity score matching (Table 1 and Table S2). Before matching, DPP4I users were more likely than US users to use metformin (37.7% versus 29.2%) and received a greater number of medications (average 14.1 versus 12.7) (Table 1 and Table S2). Propensity score matching yielded 1,008 DPP4I users and 1,008 SU users (Table 1). The mean (SD) age was 81 (8) years, 72% were female, and 37% had received metformin. Matching balanced covariates well. All but two characteristics (bladder incontinence and percent of private pay clients in the NH) were within an absolute standardized mean difference of 0.06 or less (Table S2). After matching, across both treatment groups, death was the most common outcome (49.1%), followed by MACE+HF (15.0%), HF (12.8%), severe hypoglycemia (3.1%), AMI (2.6%), and severe hyperglycemia (2.1%).

Treatment Effects

Through one year of follow-up after propensity score matching, DPP4I users had a lower rate of severe hypoglycemic events than SU users (HR: 0.57, 95%CI 0.34-0.94)(Figure 1, Table 2, and Supplementary Figure S2). The rates of severe hyperglycemic events were statistically similar between the two groups (HR: 0.94, 95%CI 0.52-1.72), as were the rates of AMI (HR 0.76, 95%CI 0.44-1.30), HF (HR 1.01, 95%CI 0.79-1.30), MACE plus HF (HR 0.90, 95%CI 0.72-1.12), and death (HR 0.97, 95% CI: 0.86-1.10)(Supplementary Figures S3-S6).

Stability and Sensitivity Analyses

The main results were generally consistent when implementing multiple imputation of missing baseline covariate information (Table S3), examining 3-month and 6-month outcomes (Table S4), estimating the propensity score using generalized boosted regression (Table S5), and employing Fine and Gray models to account for the competing risk of death (Table S6). Of note, the estimates from the generalized boosted regression propensity score-matched cohort suggested a relative reduction in death for DPP4I versus SU use at 6 months (HR 0.83, 95%CI 0.70-0.99) and 1 year (HR 0.83, 95%CI 0.73-0.95). For the main severe hypoglycemia estimate, the E-value was 2.9 for the point estimate and 1.32 for the confidence interval, suggesting results were moderately robust to confounding given the large number of measured covariates addressed in the analyses.

DISCUSSION

In this large national cohort study of NH residents, we observed a decreased rate of severe hypoglycemic events among new users of DPP4Is compared to new users of SUs through 365-days of follow-up. We did not observe any differences in the risk of severe hyperglycemia, AMI, heart failure, MACE plus heart failure, or death between the

two treatment groups. There are no known prior observational or interventional studies of the comparative effects of DPP4Is and SUs for any outcomes among NH residents. However, it is notable that the 2019 results of the CAROLINA trial comparing linagliptin and glimepiride are consistent with our findings despite arising from a younger, less complex population.[5, 6] The CAROLINA trial demonstrated no differences in major adverse cardiovascular outcomes or death, but showed a markedly lower rate of moderate or severe hypoglycemia for linagliptin users versus SU users (HR 0.18, 95%CI 0.15-0.21).[5, 6] Our results may also complement forthcoming results from the "Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study" (GRADE) pragmatic trial, which will compare outcomes for DPP4I and SU users and may have included some NH residents despite its exclusion of clinically or medically unstable individuals with an expected survival of less than one year.[15] Since minimizing hypoglycemia is typically the most important goal in NH residents, and there is no difference in cardiovascular outcomes, our study supports the selection of DPP4Is over SUs whenever possible for this population.

Limitations

Our results must be interpreted in light of at least two key limitations. First, because this study was observational, we cannot rule out the possibility of residual confounding (e.g., by HbA1c or other measures of glycemic control unmeasured in our data). Second, there may be under-ascertainment of outcomes in claims data for NH residents. Many occurrences of hypoglycemia and hyperglycemia will not require a hospitalization or ED visit because the NH staff are capable of managing all but the most severe occurrences. If misclassification is non-differential by treatment group and the specificity of claims-based measures is high, relative effect measures are unlikely to be biased. Finally, we did not quantify the as-treated estimand as a causal contrast because we did not have medication administration record data to classify person-time spent "on drug" with very high accuracy.

Summary

Use of DPP4Is for T2DM among older NH residents may result in a lower risk of severe hypoglycemia compared to use of SUs but is not associated with a differential risk of severe hyperglycemia, AMI, heart failure, MACE plus heart failure, or death. Additional studies are needed to better understand the comparative safety and effectiveness of other newer glucose-lowering treatments in the NH setting, especially sodium-glucose co-transporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) agonists. However, our study provides new evidence to guide treatment decisions for NH residents and other frail older adults with T2DM, supporting the use of DPP4Is as a preferred treatment over SUs to decrease severe hypoglycemia risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points:

- Dipeptidyl peptidase-4 inhibitors (DPP4Is) reduced the risk of severe hypoglycemia by 43% compared to sulfonylureas (SUs) among older nursing home (NH) residents.
- No differences were observed in hyperglycemia, cardiovascular, or death outcomes.

Why does this matter? DPP4Is should be a preferred treatment over SUs for long-stay NH residents.

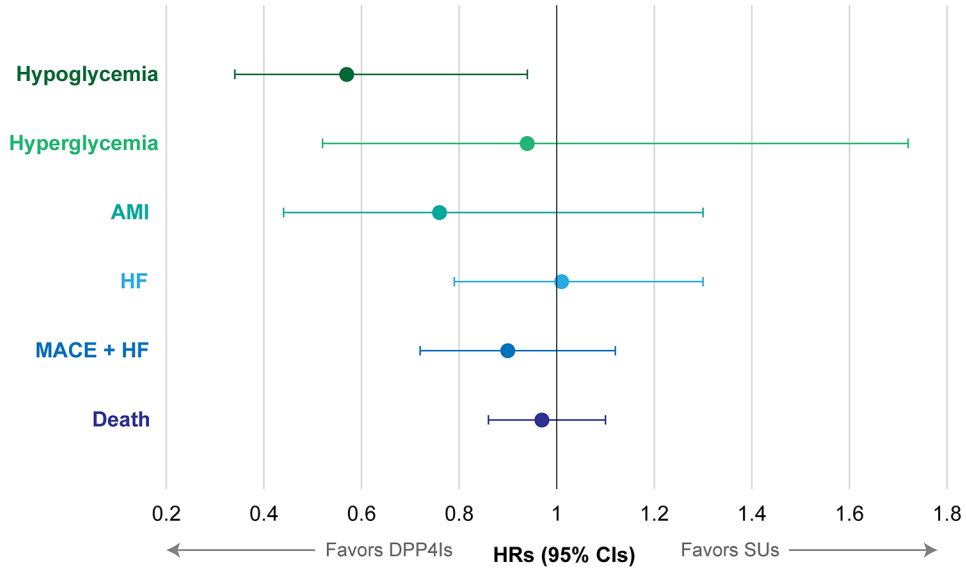

Figure 1.

Effects of Dipeptidyl Peptidase-4 Inhibitors versus Sulfonylureas on One-year Outcomes After Propensity Score Matching among Nursing Home Residents. Abbreviations: DPP4I, dipeptidyl peptidase-4 inhibitor; SU, sulfonylurea; AMI, acute myocardial infarction; MACE, major adverse cardiovascular events; HF, heart failure.

Table 1.

Characteristics of Nursing Home Residents Initiating Dipeptidyl Peptidase-4 Inhibitors or Sulfonylureas Before and After Propensity Score Matching.

	n (%)			
	Before Matching		After Matching	
Resident Characteristics	**DPP4I users (N=1,064)**	**SU users (N=6,821)**	**DPP4I users (N=1,008)**	**SU users (N=1,008)**
Age, mean (SD) years	80.4 (8.1)	81.4 (8.2)	80.5 (8.1)	80.6 (8.1)
Female sex	766 (72.0)	4,816 (70.6)	725 (71.9)	732 (72.6)
Race				
White	773 (72.7)	5,164 (75.7)	742 (73.6)	726 (72.0)
Black	165 (15.5)	1,066 (15.6)	159 (15.8)	167 (16.6)
Other	126 (11.8)	591 (8.7)	107 (10.6)	115 (11.4)
Conditions				
Renal disease	115 (10.8)	639 (9.4)	103 (10.2)	108 (10.7)
Peripheral vascular disease	195 (18.3)	1,150 (16.9)	180 (17.9)	171 (17.0)
Diabetic retinopathy	19 (1.8)	132 (1.9)	18 (1.8)	20 (2.0)
Heart failure	338 (31.8)	1,934 (28.4)	315 (31.3)	331 (32.8)
Ischemic heart disease	198 (18.6)	1,039 (15.2)	177 (17.6)	204 (20.2)
Depression	596 (56.0)	3,818 (56.0)	566 (56.2)	575 (57.0)
Chronic Obstructive Pulmonary Disease	230 (21.6)	1,365 (20.0)	215 (21.3)	217 (21.5)
Hypertension	812 (76.3)	5,261 (77.1)	774 (76.8)	783 (77.7)
Hip fracture	17 (1.6)	121 (1.8)	17 (1.7)	18 (1.8)
Number of conditions, median, (IQR)	6 (4-8)	5 (4-7)	6 (4-7)	6 (4-8)
ADL score, mean (SD)[†]	15.8 (7.6)	15.8 (7.7)	15.8 (7.6)	16.1 (7.4)
CPS score, mean (SD)[‡]	2.4 (1.6)	2.6 (1.6)	2.5 (1.6)	2.5 (1.6)
CHESS score, mean (SD)[§]	0.5 (0.8)	0.5 (0.8)	0.5 (0.8)	0.5 (0.8)
Number of medications, mean (SD)	14.1 (5.2)	12.7 (4.8)	13.9 (5.0)	13.8 (5.0)
Medication use				
Metformin	401 (37.7)	1,992 (29.2)	370 (36.7)	379 (37.6)
Statins	487 (45.8)	2,680 (39.3)	450 (44.6)	448 (44.4)
Clopidogrel	214 (20.1)	959 (14.1)	194 (19.3)	215 (21.3)
Warfarin	169 (15.9)	1,015 (14.9)	161 (16.0)	168 (16.7)
Antipsychotics	330 (31.0)	2,000 (29.3)	313 (31.1)	279 (27.7)
Steroids (oral)	138 (13.0)	857 (12.6)	128 (12.7)	122 (12.1)
Angiotensin-converting enzyme inhibitors	455 (42.8)	2,578 (37.8)	423 (42.0)	437 (43.4)
Angiotensin receptor blockers	169 (15.9)	758 (11.1)	146 (14.5)	151 (15.0)
Beta blockers	543 (51.0)	3,063 (44.9)	507 (50.3)	528 (52.4)
Length of nursing home stay before treatment initiation, median (IQR) days	647 (296-1,305)	589 (273-1,181)	649 (295-1,296)	640 (294-1,225)
Any physician visits in prior two weeks	639 (60.0)	3,948 (57.9)	595 (59.0)	589 (58.4)
Number of physician order changes in prior two weeks, mean (SD)	2.1 (2.0)	1.9 (1.8)	2.0 (1.9)	2.1 (1.9)

	n (%)			
	Before Matching		After Matching	
Resident Characteristics	**DPP4I users (N=1,064)**	**SU users (N=6,821)**	**DPP4I users (N=1,008)**	**SU users (N=1,008)**
Any overnight hospitalizations in prior 90 days	335 (31.5)	2,011 (29.5)	316 (31.4)	319 (31.7)
Any ED visits in prior 90 days	80 (7.5)	541 (7.9)	76 (7.5)	73 (7.2)
Nursing Home Facility Characteristics				
Ownership				
For profit	771 (72.5)	4,835 (70.9)	735 (72.9)	758 (75.2)
Non-profit	231 (21.7)	1,514 (22.2)	215 (21.3)	189 (18.8)
Government	62 (5.8)	472 (6.9)	58 (5.8)	61 (6.1)
Quality indicators				
% of residents restrained, median (IQR)	1.9 (0.0-5.1)	1.8 (0.0-4.7)	2.0 (0.0-5.1)	1.9 (0.0-5.1)
No. of quality-of-life deficiencies, mean (SD)	4.1 (6.1)	3.8 (6.9)	4.0 (6.1)	4.2 (10.0)
% of residents with pressure sores, mean (SD)	6.9 (4.3)	6.6 (4.2)	6.8 (4.3)	6.8 (4.5)
Staffing				
Direct care hours/resident/day, mean (SD)	2.9 (1.2)	2.9 (1.3)	2.8 (1.2)	2.9 (1.2)

† Physical function was measured using activities of daily living (ADL) via the Minimum Data Set Morris 28-point ADL score. The ADL scores range from 0 to 28, with 0 indicating total independence and 28 indicating total dependence in all ADLs.

‡ Cognitive status was measured using the Minimum Data Set Cognitive Performance Scale (CPS), where higher values indicate greater cognitive impairment. The CPS scores range from 0 to 6, with 0 indicating intact cognitive function and 6 indicating very severe cognitive impairment.

§ The Minimum Data Set Changes in Health, End-stage disease and Symptoms and Signs (CHESS) score is a composite measure addressing changes in health, end-stage disease, and symptoms and signs of medical problems. The CHESS scores range from 0 to 5, with 0 indicating no health instability and 5 indicating very high health instability.

Table 2:

Effects of Dipeptidyl Peptidase-4 Inhibitors versus Sulfonylureas on One-year Outcomes Before and After Propensity Score Matching.

		Before Matching				After Matching			
Outcome	**Treatment**	**Events**	**PY**	**Rate***	**HR (95% CI)**	**Events**	**PY**	**Rate***	**HR (95% CI)**
Hypoglycemia	SU	207	5,052.3	41.0	Ref	40	739.0	54.1	Ref
	DPP4I	24	756.7	31.7	0.78 (0.51-1.18)	23	747.6	30.8	0.57 (0.34-0.94)
Hyperglycemia	SU	142	5,067.4	28.0	Ref	22	743.6	29.6	Ref
	DPP4I	21	758.7	27.7	0.99 (0.63-1.57)	21	749.6	28.0	0.94 (0.52-1.72)
AMI	SU	155	5,078.4	30.5	Ref	30	744.9	40.3	Ref
	DPP4I	23	760.9	30.2	0.99 (0.64-1.53)	23	751.8	30.6	0.76 (0.44-1.30)
HF	SU	726	4,946.1	146.8	Ref	127	723.3	175.6	Ref
	DPP4I	131	736.7	177.8	1.21 (1.01-1.46)	130	727.8	178.6	1.01 (0.79-1.30)
MACE + HF	SU	862	4,924.8	176.4	Ref	158	717.9	220.0	Ref
	DPP4I	147	735.4	203.5	1.14 (0.96-1.36)	144	726.7	198.2	0.90 (0.72-1.12)
Death	SU	3,124	5,186.3	602.4	Ref	501	749.2	668.7	Ref
	DPP4I	523	789.6	662.4	1.10 (1.00-1.21)	488	753.7	647.5	0.97 (0.86-1.10)

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

Abbreviations: PY, person-years; SU, sulfonylurea; DPP4I, dipeptidyl peptidase-4 inhibitor; AMI, acute myocardial infarction; MACE, major adverse cardiovascular events; HF, heart failure.

Note: In the initial design of the study, we had planned to examine the 365-day outcome for stroke, but preliminary analyses of the study data demonstrated that there were too few outcome events and reporting them would have violated the CMS's Cell Size Suppression Policy governing our use of the data.