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The Impact of Metformin Use on the Cardiovascular Effects of DPP-4 Inhibitors: an Analysis of Medicare Claims Data 2007–2015

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Abstract

Aims: Metformin may moderate cardiovascular outcomes with dipeptidyl peptidase-4 inhibitors (DPP-4i). We examined outcomes of DPP-4i initiation with and without concurrent metformin.

Materials and Methods: We identified Medicare enrollees initiating DPP-4i, sulfonylurea, or thiazolidinedione. Using propensity score-weighted Poisson models, we evaluated one-year cardiovascular outcome incidence among initiators of DPP-4i versus comparators in subgroups with and without concurrent metformin use, and assessed the interaction between initiation drug and metformin. Outcomes included mortality, non-fatal myocardial infarction (MI), stroke, and a composite.

Results: For the DPP-4i (n=13,391) versus sulfonylurea (n=33,206) comparison, rate differences in composite outcome incidence favored DPP-4i: −2.0/100 person-years among metformin users (95%CI: −2.7,−1.3) and −1.0 (−1.8,−0.2) among metformin non-users. Similar rate difference trends among metformin users and non-users were seen for mortality (−1.5 (−2.1,−0.9) and −0.7 (−1.4,0.0)) and non-fatal MI (−0.5 (−0.8,−0.3) and 0.1 (−0.2,0.4)). The interaction between DPP-4i initiation and metformin was statistically significant for non-fatal MI (p=0.008). For the DPP-4i (n=22,210) versus thiazolidinedione (n=9,517) comparison, rate differences in composite outcome incidence for DPP-4i initiation were −0.6/100 person-years (−1.5,0.2) among metformin users and 1.0 (0.0,2.0) among metformin non-users. Similar rate difference trends among metformin users and non-users were seen for mortality (−0.5 (−1.3,0.1) and 0.8 (−0.0,1.7)) and

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non-fatal MI (−0.1 (−0.4,0.2) and 0.2 (−0.1,0.6)). The interaction between DPP-4i initiation and metformin was statistically significant for the composite (p=0.024) and mortality (p=0.023).

Conclusions: Incidence rate differences in multiple cardiovascular outcomes appeared more favorable when DPP-4i initiation occurred in the presence of metformin, suggesting a possible interaction between DPP-4i and metformin.

Introduction

Metformin is the recommended initial treatment for type 2 diabetes mellitus.(1) Beyond its glycemic benefits, metformin does not cause weight gain or hypoglycemia, and may be associated with lower mortality.(2,3) Because other diabetes medications are typically added to a foundation of metformin therapy, understanding how concurrent metformin use affects outcomes with initiation of other agents is important. Currently, interactions between metformin and other diabetes medications are poorly understood. Recent years have seen the advent of multiple new medication classes for diabetes, raising the urgency of understanding how metformin and newer agents interact to affect cardiovascular (CV) outcomes.

Based on a meta-analysis of three CV outcomes trials,(4–6) we recently reported a possible interaction between dipeptidyl peptidase-4 inhibitors (DPP-4i) and metformin.(7) While concurrent metformin users experienced a trend toward improved CV outcomes with DPP-4i use (summary HR 0.92, 95% CI 0.84 to 1.01), metformin non-users showed a trend towards harm (HR 1.10, 95% CI 0.97 to 1.26). The difference in overall DPP-4i effect between metformin user and non-user subgroups was statistically significant (p=0.036). Because there is a physiologic mechanism by which metformin could potentiate the effect of DPP-4i – metformin raises levels of glucagon-like peptide-1 (GLP-1),(8,9) and DPP-4i inhibit GLP-1 degradation – it is plausible that the two drugs could interact synergistically.

While this novel, hypothesis-generating analysis suggested that metformin use may be a moderator of DPP-4i effect on CV outcomes, it had limitations. First, because patient-level data were unavailable, we could not account for important potential baseline differences between metformin users and non-users. Second, we could not evaluate the moderating effects of metformin while comparing DPP-4i to specific alternative agents.

In order to continue exploring the possible interaction between DPP-4i and metformin, we used Medicare claims data to examine CV outcomes with initiation of DPP-4i versus two other common second-line diabetes therapies (sulfonylurea or thiazolidinedione), both in the presence and absence of concurrent metformin use. We then evaluated the statistical interaction between drug initiation choice and concurrent metformin use in the overall population. Our goal was to examine metformin's possible moderating effect on CV outcomes with DPP-4i initiation, while considering potential baseline population differences and specific therapeutic alternatives.

Materials and Methods

This retrospective, new-user, active comparator cohort study examined Medicare claims data containing longitudinal information about demographics, enrollment, diagnoses, procedures, prescription drugs, and mortality for each enrollee.

Study Population

Our study population derived from a 20% random sample of Medicare beneficiaries generated by the Centers for Medicare and Medicaid Services (CMS). We identified patients aged >65 years with fee-for-service Part A, B, and D enrollment during at least 1 month between January 1, 2007 to December 31, 2015. We constructed 4 new-user, active comparator cohort pairs after a 1-year washout period: 1) initiators of DPP-4i or sulfonylurea with concurrent metformin use; 2) initiators of DPP-4i or sulfonylurea without concurrent metformin use; 3) initiators of DPP-4i or thiazolidinedione with concurrent metformin use; and 4) initiators of DPP-4i or thiazolidinedione without concurrent metformin use. Specific agents included sitagliptin, saxagliptin, linagliptin, and alogliptin (DPP-4i); glyburide, glipizide, and glimepiride (sulfonylurea); and pioglitazone and rosiglitazone (thiazolidinedione).

We defined each patient's index date as the first prescription of the drug class of interest (DPP-4i, sulfonylurea, or thiazolidinedione) after a 12-month washout. For each active comparator cohort pair, prevalent users of the drug classes of interest were excluded. To reduce the potential for secondary non-adherence or discontinuation, we restricted our cohorts to patients with a second prescription from the originally initiated drug class within 6 months of the index date. Patient follow-up began at this second fill date. Patients were required to have at least 12 months of continuous Medicare Part A, B and D enrollment before initiation. Patients with concurrent metformin use were defined as those with days-supply of metformin on the index date and on the date of the second prescription. Patients with no concurrent metformin use were defined as those with no days-supply of metformin on the index date and no days-supply plus a grace period (0.5*days-supply of the metformin prescription) on the second prescription date. Patients not meeting either of these profiles were excluded.

The decision to prescribe metformin may be affected by chronic kidney disease (CKD), congestive heart failure (CHF), and long-acting insulin use, potentially leading to confounding population differences between concurrent metformin users and non-users. In order to: 1) minimize differences between metformin users and non-users; and 2) reduce confounding by contraindication in comparing initiation of DPP-4i versus alternative agents, we excluded patients with CKD, CHF (including edema, cardiomyopathy, arrhythmia, and loop diuretic use), or use of long-acting insulin during the 12 months prior to the index date. Supplemental Table 1 lists the International Classification of Diseases, Ninth Revision (ICD-9) and Current Procedural Terminology (CPT) codes used in excluding patients with CKD and CHF.

Covariates

Baseline covariates were examined during the 12 months prior to the index date (inclusive of the index date). We examined demographic data, including age, gender, and race/ethnicity. We also assessed comorbidities, concurrent use of relevant medications (i.e., the proportion of patients with ≥1 prescription during the 12 months prior to the index date) and healthcare utilization. Full lists of comorbidity, medication and healthcare utilization covariates are provided in Tables 1 and 2.

Outcomes and follow-up

Patient follow-up began at the date of the second prescription for the drug class being initiated (DPP-4i versus alternative) and ended at the earliest of the following events: outcome occurrence; treatment discontinuation; switching or augmentation; change in metformin use status allowing for a grace period of 0.5*days-supply; the end of the 12-month follow-up period; or December 31, 2015.

Outcomes of interest included a composite of all-cause mortality, non-fatal myocardial infarction (MI), and stroke; we chose this outcome in order to replicate the primary outcome utilized by recent Food and Drug Administration-mandated CV outcomes trials (4–6). Because Medicare claims do not include information on cause of death, we used all-cause mortality as a proxy for CV death in our composite; CV deaths account for >50% of all-cause mortality in patients with diabetes. We also individually evaluated all-cause mortality, as well as non-fatal MI, and stroke (censoring for mortality). We used validated ICD-9-based definitions for non-fatal MI (code 410 in the first or second position of inpatient claims) and stroke (codes 430, 431, 433.x1, 434.x1, or 436 in the first position of inpatient claims). (10,11)

Analysis

In order to determine whether metformin is a moderator of CV outcomes with initiation of DPP-4i, we first compared DPP-4i to each active comparator agent (sulfonylurea or thiazolidinedione) using separate, weighted Poisson regression models in subgroups with and without concurrent metformin use. Using all baseline covariates, we created logistic regression models to estimate subgroup-specific propensity scores predicting initiation of DPP-4i versus sulfonylurea in the presence and absence of concurrent metformin, and DPP-4i versus thiazolidinedione in the presence and absence of metformin.(12) In each analysis, we assigned a weight of ‘1’ to DPP-4i initiators and a weight of ‘propensity score/[1 − propensity score]’ to initiators of sulfonylurea or thiazolidinedione. This created pseudo-populations of patients initiating sulfonylurea and thiazolidinedione with similar covariate distribution to those initiating DPP-4i.(13,14) Each weighted Poisson regression model utilized a bootstrap variance estimator to determine 95% confidence intervals for CV outcome rate differences. These analyses thus explored what would have happened to DPP-4i initiators had they instead initiated sulfonylurea or thiazolidinedione, both in the presence and absence of concurrent metformin.(15)

Next, we evaluated interaction terms between drug initiation choice (DPP-4i versus sulfonylurea or DPP-4i versus thiazolidinedione) and concurrent metformin use in each

population. Interaction analyses were based on the weighted 12-month absolute rate differences between DPP-4i and comparator estimated using weighted Poisson regression models, with propensity scores estimated in the overall population with or without concurrent metformin.

Sensitivity Analyses

Prescribing patterns in diabetes have changed over time,(16) which could have affected drug initiation patterns and CV outcomes during the study period. We therefore conducted sensitivity analyses adjusting for the impact of calendar year. In these analyses, we re-estimated propensity scores accounting for calendar year of initiation, and recalculated CV outcome rate differences for DPP-4i versus comparators (using methods above) with the re-estimated propensity scores. Of note, we did not adjust for calendar year in our primary analysis because we have previously suggested that calendar year is an instrumental variable in studies of CV outcomes with initiation of DPP-4i versus thiazodinedione;(17) conditioning for instrumental variables in propensity scores can increase bias and variance, so should be avoided.(18–20)

Results

Baseline Characteristics

For the DPP-4i versus sulfonylurea comparison, we identified 8,665 DPP-4i initiators and 18,420 sulfonylurea initiators with concurrent metformin use. Among metformin non-users, we identified 4,726 DPP-4i initiators and 14,786 sulfonylurea initiators. Baseline characteristics were generally similar between initiators of DPP-4i and sulfonylurea within each metformin subgroup and any remaining differences were balanced by weighting using subgroup-specific propensity scores (Table 1).

For the DPP-4i versus thiazolidinedione comparison, we identified 15,141 DPP-4i initiators and 5,983 thiazolidinedione initiators with concurrent metformin use. Among metformin non-users, we identified 7,069 DPP-4i initiators and 3,834 thiazolidinedione initiators. Baseline characteristics were generally similar between initiators of DPP-4i and thiazolidinedione within each metformin subgroup and any remaining differences were balanced by weighting (Table 2).

Incidence of CV outcomes with initiation of DPP-4i versus sulfonylurea among concurrent metformin users and non-users

For the comparison of DPP-4i versus sulfonylurea, outcomes generally favored DPP-4i initiation regardless of metformin use (Table 3). One-year incidence of the composite outcome ranged from 3.4–5.6 per 100 person-years across groups; the rate difference with DPP-4i versus sulfonylurea was −2.0 per 100 person-years (95% CI: −2.7 to −1.3) among metformin users and −1.0 (−1.8 to −0.2) among metformin non-users. For all-cause mortality, one-year incidence ranged from 2.6–4.4 per 100 person-years across groups; the rate difference with DPP-4i versus sulfonylurea was −1.5 per 100 person-years (−2.1 to −0.9) among metformin users and −0.7 (−1.4 to 0.0) among metformin non-users. For non-fatal MI, one-year incidence ranged from 0.4–1.0 per 100 person-years across groups; the

rate difference with DPP-4i versus sulfonylurea was −0.5 per 100 person-years (−0.8 to −0.3) among metformin users and 0.1 (−0.2 to 0.4) among metformin non-users. For stroke, one-year incidence ranged from 0.3–0.8 per 100 person-years across groups; the rate difference with DPP-4i versus sulfonylurea was −0.1 per 100 person-years (−0.3 to 0.1) among metformin users and −0.5 (−0.7 to −0.2) among metformin non-users.

For the composite outcome, mortality, and non-fatal MI, rate differences appeared to more strongly favor DPP-4i initiation (over sulfonylurea) among concurrent metformin users. The interaction between drug initiation choice and metformin use was statistically significant for non-fatal MI (p=0.008) (Table 4). Thus, patients initiating DPP-4i rather than sulfonylurea experienced a significantly more favorable rate difference for non-fatal MI with concurrent metformin than in the absence of metformin.

Initiation of DPP-4i versus thiazolidinedione among concurrent metformin users and non-users

For the comparison of DPP-4i versus thiazolidinedione, most outcomes trended toward favoring DPP-4i initiation among concurrent metformin users, and toward thiazolidinedione initiation among metformin non-users (Table 3). For the composite outcome, one-year incidence ranged from 3.4–4.5 per 100 person-years across groups; the rate difference with DPP-4i versus thiazolidinedione was −0.6 per 100 person-years (95% CI: −1.5 to 0.2) among concurrent metformin users and 1.0 (0.0 to 2.0) among metformin non-users. One-year incidence of all-cause mortality ranged from 2.4–3.5 per 100 person-years across groups; the rate difference with DPP-4i versus thiazolidinedione was −0.5 per 100 person-years (−1.3 to 0.1) among metformin users and 0.8 (−0.0 to 1.7) among metformin non-users. For non-fatal MI, one-year incidence ranged from 0.6–0.8 per 100 person-years across groups; the rate difference with DPP-4i versus thiazolidinedione was −0.1 per 100 person-years (−0.4 to 0.2) among metformin users and 0.2 (−0.1 to 0.6) among metformin non-users. One-year stroke incidence ranged from 0.5–0.7 per 100 person-years across groups, but rates did not differ between DPP-4i and thiazolidinedione initiators regardless of metformin use.

For the composite outcome, mortality, and non-fatal MI, rate differences appeared to favor DPP-4i initiation (over thiazolidinedione) among concurrent metformin users. The interaction between drug initiation choice and metformin use was statistically significant for the composite outcome (p=0.024) and all-cause mortality (p=0.023) (Table 4). Thus, patients initiating DPP-4i rather than thiazolidinedione experienced significantly more favorable rate differences for the composite outcome and mortality with concurrent metformin than in the absence of metformin.

Sensitivity Analyses

Results from the sensitivity analyses incorporating adjustment for initiation year yielded similar results for the DPP-4i versus sulfonylurea comparison. Results for the DPP-4i versus thiazolidinedione comparison varied modestly in magnitude and precision for most outcomes, but also changed direction in some cases (Supplemental Table 2); for example, among concurrent metformin users, the one-year rate difference for the composite outcome

was −0.6 per 100 person-years (−1.5 to 0.2) favoring DPP-4i in the primary analysis, but changed to 0.2 (−0.8 to 1.1) favoring thiazolidinedione in the sensitivity analysis adjusting for calendar year.

Discussion

This analysis explored whether concurrent metformin use moderates the effect of DPP-4i initiation on CV outcomes. Initiating DPP-4i rather than sulfonylurea was associated with lower one-year rates of multiple CV outcomes overall, but rate differences more strongly favored DPP-4i in the presence of metformin. For non-fatal MI, the interaction between drug initiation choice and metformin use was statistically significant. Initiating DPP-4i rather than thiazolidinedione was associated with favorable rate differences for multiple CV outcomes in the presence of concurrent metformin, but unfavorable rate differences in the absence of metformin. For the composite outcome and all-cause mortality, the interaction between drug initiation choice and metformin use was statistically significant. Overall, these hypothesis-generating findings support the possibility that CV outcomes with DPP-4i may be more favorable in the presence of metformin than in its absence.

Sensitivity analyses adjusting for calendar year of initiation did not meaningfully change results for the DPP-4i versus sulfonylurea comparison, but did affect results for some outcomes for the DPP-4i versus thiazolidinedione comparison. We have previously reported that calendar year strongly predicts initiation of DPP-4i versus thiazolidinedione and argued for its use as instrumental variable with respect to CV outcomes; therefore, the observed changes in our sensitivity analyses can be explained by adjustment for the calendar year instrument.(18) It is for this reason that we did not include calendar year in our primary analyses.

Our findings regarding interactions between drug initiation choice (DPP-4i versus alternatives) and metformin status are consistent with – and could potentially underlie – the results of our recent meta-analysis.(7) The present analysis used real-world data and rigorous methodology to build upon our prior findings by addressing weaknesses of the meta-analysis. We minimized important potential population differences between metformin users and non-users by restricting to patients without CKD, CHF and long-acting insulin use. Our use of restriction and a new-user, active comparator design helps balance baseline risk of outcomes and key confounders, and also likely reduces unmeasured confounding. Further remaining imbalances in measured covariates were mitigated by using propensity score-based weighting. We were also able to explore the interaction between DPP-4i initiation and metformin status with consideration of individual comparator agents and specific CV outcomes.

Prior randomized trials have indicated that DPP-4i exert a neutral effect on CV outcomes versus placebo.(4–6,21) While an ongoing trial is comparing the effects of a DPP-4i (linagliptin) and a sulfonylurea (glimepiride) on CV outcomes,(22) randomized trial data comparing DPP-4i to active comparators are limited. Consistent with our current findings, multiple observational studies have suggested that DPP-4i may be associated with improved CV outcomes relative to sulfonylurea.(23–25) Also consistent with our results, observational

studies show similar rates of CV outcomes with DPP-4i and thiazolidinedione,(24) or even increased rates of some outcomes with DPP-4i.(26,27) However, prior studies have not specifically examined how metformin interacts with DPP-4i to affect outcomes. Our findings therefore extend the existing literature by exploring the interaction between DPP-4i and metformin.

Although the average treatment effect of DPP-4i in randomized trials appears neutral, it is increasingly understood that trial-reported average treatment effects often conceal variability in results experienced by patient subgroups.(28,29) One potential contributor to heterogeneity of treatment effect in diabetes trials is interactions between co-prescribed medications. Currently, how different medication classes interact to determine CV outcomes in type 2 diabetes is poorly understood. Since metformin is the consensus first-line medical treatment for type 2 diabetes,(1) recognizing how its presence impacts the effectiveness of next-line agents like DPP-4i could inform clinical practice and guideline development. Because there exists a potential GLP-1-based mechanism by which metformin could enhance the effect of DPP-4i,(8,9) DPP-4i provide a sensible opportunity to study interactions with metformin.

For multiple CV outcomes, initiation of DPP-4i rather than sulfonylurea was associated with a more pronounced risk difference in the presence of metformin; the interaction between drug initiation choice and concurrent metformin status was statistically significant for non-fatal MI. Similarly, initiation of DPP-4i rather than thiazolidinedione tended to be associated with more favorable risk differences in the presence of metformin; the interaction between drug initiation choice and concurrent metformin status was statistically significant for the composite outcome and all-cause mortality. Taken together, these findings provide support for the concept that physiologic interactions between certain medication classes may affect specific CV outcomes and contribute to the heterogeneity of treatment effect seen in randomized trials. If confirmed, our results may provide a rationale for using DPP-4i specifically in conjunction with metformin.

While our findings offer support for a possible advantageous interaction between DPP-4i and metformin, an alternative interpretation is that metformin could instead have deleterious interactions with the comparator agents. The higher absolute rates of the composite outcome and mortality among sulfonylurea and thiazolidinedione initiators with concurrent metformin use (as compared to initiators without concurrent metformin) may support this alternative. Observational studies suggest that the combination of metformin and sulfonylurea may be associated with higher CV risk,(30) and early addition of metformin to sulfonylurea was associated with increased risk of death in the United Kingdom Prospective Diabetes Study.(31) We know of no analogous data regarding the combination of metformin and thiazolidinedione. While a deleterious metformin-comparator interaction cannot be dismissed, the physiologic plausibility of a favorable interaction between DPP-4i and metformin, along with the general consistency of our sulfonylurea and thiazolidinedione analyses, supports our primary interpretation.

Limitations

We focused exclusively on Medicare beneficiaries aged >65 years with fee-for-service Part A, B, and D enrollment, which may limit the generalizability of our findings. Because we specifically examined new users of DPP-4i and comparator drugs in order to minimize prevalent-user biases, our findings likewise may not generalize to patients on complex regimens.

Although we minimized important differences between metformin users and non-users by attempting to exclude patients with CKD, CHF, and long-acting insulin use, individuals with mild and/or unrecognized CKD or CHF may have been included in our analytic sample. Other unaccounted-for differences between metformin users and non-users may also have been present. It is therefore possible that factors other than metformin use alone may explain the observed differences in DPP-4i effect between concurrent metformin users and non-users.

Medicare claims do not contain variables like body mass index and smoking, so we were unable to directly adjust for these factors in examining the relationship between drug initiation choice and CV outcomes. However, previous studies have shown that these variables do not affect the choice to initiate of DPP-4i versus sulfonylurea or thiazolidinedione,(32) so are unlikely to be strong confounders. In this Medicare population, mortality contributed strongly to our composite outcome. We did not account for intervening mortality when examining the risk of individual CV outcomes at one year.

We used ICD-9 codes to ascertain non-fatal MI and stroke events in this study. CMS implemented use of the International Classification of Diseases, Tenth Revision (ICD-10) on October 1, 2015. As such, some unaccounted-for non-fatal MI and stroke events may have occurred during the final 3 months of the 2007–2015 observation period. This issue did not impact mortality ascertainment, and is unlikely to have substantively affected our findings. Additionally, we confined follow-up to 12 months. While this choice minimizes the likelihood of undetected secondary non-adherence or downstream discontinuation, restricting follow-up may have limited detection of between-group differences that emerge over time.

Of note, specific agents within the DPP-4i class may interact with metformin differently. Future research should further examine metformin’s moderating effects on individual DPP-4i agents, and also explore how metformin may interact with other novel medication classes.

Conclusions

Consistent with the findings from our recent meta-analysis, we found evidence for interactions between drug initiation choice (DPP-4i versus alternative agents) and concurrent metformin use with regard to some CV outcomes. Beyond the potential clinical implications of metformin’s potential moderating effect on CV outcomes with DPP-4i initiation, this analysis supports the concept that physiologic interactions between medication classes may affect outcomes, and argues for further investigation of interactions between commonly-used medications for type 2 diabetes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Baseline characteristics for DPP-4i initiators, sulfonylurea initiators, and subgroup weighted sulfonylurea initiators (with subgroup-weighted standardized mean differences), stratified by concurrent metformin use and metformin non-use.

Characteristic	Concurrent metformin users				Concurrent metformin non-users			
	DPP-4i N=8,665	Overall SU N=18,420	Subgroup Weighted SU N=8,660	Subgroup Weighted SMD	DPP-4i N=4,726	Overall SU N=14,786	Subgroup Weighted SU N=4,739	Subgroup Weighted SMD
Demographics								
Age, mean(SD)	71.6(3.74)	71.4(3.78)	71.4(3.78)	0.046	72.3(3.92)	72.3(4.00)	72.3(4.00)	0.008
Male sex	3,946 (45.5%)	9,145 (49.6%)	3,932 (45.4%)	0.003	1,858 (39.3%)	6,524 (44.1%)	1,859 (39.2%)	0.002
Race								
Other	1,329 (15.3%)	2,331 (12.7%)	1,309 (15.1%)	0.006	687 (14.5%)	1,446 (9.8%)	673 (14.2%)	0.009
White	6,705 (77.4%)	14,461 (78.5%)	6,720 (77.6%)	0.005	3,562 (75.4%)	11,550 (78.1%)	3,587 (75.7%)	0.007
Black	631 (7.3%)	1,628 (8.8%)	632 (7.3%)	0.001	477 (10.1%)	1,790 (12.1%)	479 (10.1%)	0.000
Comorbidities								
Acute myocardial infarction	55 (0.6%)	136 (0.7%)	56 (0.6%)	0.001	34 (0.7%)	124 (0.8%)	33 (0.7%)	0.002
Old myocardial infarction	164 (1.9%)	391 (2.1%)	162 (1.9%)	0.001	84 (1.8%)	309 (2.1%)	85 (1.8%)	0.001
Angina	272 (3.1%)	454 (2.5%)	268 (3.1%)	0.003	153 (3.2%)	376 (2.5%)	149 (3.1%)	0.006
Dyslipidemia	7,216 (83.3%)	14,395 (78.1%)	7,221 (83.4%)	0.003	3,801 (80.4%)	10,792 (73.0%)	3,812 (80.4%)	0.000
Hypertension	7,273 (83.9%)	15,231 (82.7%)	7,266 (83.9%)	0.001	3,938 (83.3%)	11,881 (80.4%)	3,940 (83.1%)	0.005
Stroke/TIA	276 (3.2%)	624 (3.4%)	274 (3.2%)	0.001	171 (3.6%)	620 (4.2%)	170 (3.6%)	0.002
Other acute/subacute IHD	97 (1.1%)	198 (1.1%)	96 (1.1%)	0.001	56 (1.2%)	153 (1.0%)	53 (1.1%)	0.007
Obesity	81 (0.9%)	161 (0.9%)	81 (0.9%)	0.001	51 (1.1%)	145 (1.0%)	51 (1.1%)	0.001
Diabetic nephropathy	193 (2.2%)	347 (1.9%)	195 (2.2%)	0.002	119 (2.5%)	209 (1.4%)	127 (2.7%)	0.010
Diabetic neuropathy	1,082 (12.5%)	1,903 (10.3%)	1,077 (12.4%)	0.001	507 (10.7%)	1,123 (7.6%)	519 (10.9%)	0.007
Diabetic retinopathy	914 (10.5%)	1,735 (9.4%)	913 (10.5%)	0.000	363 (7.7%)	880 (6.0%)	359 (7.6%)	0.004
Atherosclerosis	440 (5.1%)	748 (4.1%)	433 (5.0%)	0.004	278 (5.9%)	700 (4.7%)	279 (5.9%)	0.000
Bone fractures	313 (3.6%)	538 (2.9%)	318 (3.7%)	0.003	187 (4.0%)	554 (3.7%)	189 (4.0%)	0.002
COPD	898 (10.4%)	1,913 (10.4%)	895 (10.3%)	0.001	599 (12.7%)	1,872 (12.7%)	598 (12.6%)	0.001
Cancer (non-skin)	1,342 (15.5%)	2,529 (13.7%)	1,352 (15.6%)	0.003	728 (15.4%)	2,266 (15.3%)	721 (15.2%)	0.005
Chronic lung diseases	983 (11.3%)	1,816 (9.9%)	973 (11.2%)	0.003	624 (13.2%)	1,635 (11.1%)	628 (13.2%)	0.001
Connective tissue diseases	2,145 (24.8%)	3,944 (21.4%)	2,132 (24.6%)	0.003	1,395 (29.5%)	3,636 (24.6%)	1,385 (29.2%)	0.006
Dementia	163 (1.9%)	432 (2.3%)	161 (1.9%)	0.001	112 (2.4%)	430 (2.9%)	112 (2.4%)	0.000
Depression	957 (11.0%)	1,859 (10.1%)	954 (11.0%)	0.001	601 (12.7%)	1,617 (10.9%)	601 (12.7%)	0.001

Characteristic	Concurrent metformin users				Concurrent metformin non-users			
	DPP-4i N=8,665	Overall SU N=18,420	Subgroup Weighted SU N=8,660	Subgroup Weighted SMD	DPP-4i N=4,726	Overall SU N=14,786	Subgroup Weighted SU N=4,739	Subgroup Weighted SMD
Foot ulcers	466 (5.4%)	971 (5.3%)	465 (5.4%)	0.001	319 (6.7%)	877 (5.9%)	323 (6.8%)	0.003
Inflammatory GI diseases	43 (0.5%)	105 (0.6%)	42 (0.5%)	0.001	48 (1.0%)	141 (1.0%)	46 (1.0%)	0.004
Liver disease	439 (5.1%)	839 (4.6%)	439 (5.1%)	0.000	316 (6.7%)	839 (5.7%)	314 (6.6%)	0.003
Other chronic IHD	1,656 (19.1%)	3,322 (18.0%)	1,651 (19.1%)	0.001	1,048 (22.2%)	2,923 (19.8%)	1,047 (22.1%)	0.002
Other neurological disorders	1,019 (11.8%)	1,972 (10.7%)	1,028 (11.9%)	0.003	608 (12.9%)	1,484 (10.0%)	616 (13.0%)	0.004
Other ocular disorders	3,508 (40.5%)	6,471 (35.1%)	3,509 (40.5%)	0.001	1,794 (38.0%)	5,075 (34.3%)	1,785 (37.7%)	0.006
Other renal disorders	87 (1.0%)	223 (1.2%)	87 (1.0%)	0.000	132 (2.8%)	359 (2.4%)	132 (2.8%)	0.001
Pancreatitis	45 (0.5%)	118 (0.6%)	44 (0.5%)	0.001	38 (0.8%)	132 (0.9%)	36 (0.8%)	0.005
PVD (claudication)	653 (7.5%)	1,167 (6.3%)	649 (7.5%)	0.002	380 (8.0%)	1,033 (7.0%)	378 (8.0%)	0.003
Proteinuria	178 (2.1%)	337 (1.8%)	180 (2.1%)	0.002	72 (1.5%)	194 (1.3%)	74 (1.6%)	0.003
Tobacco use diagnosis	691 (8.0%)	1,539 (8.4%)	693 (8.0%)	0.001	413 (8.7%)	1,310 (8.9%)	419 (8.8%)	0.004
UTI/cystitis	1,318 (15.2%)	2,567 (13.9%)	1,317 (15.2%)	0.000	848 (17.9%)	2,179 (14.7%)	838 (17.7%)	0.007
Upper respiratory disorders	2,171 (25.1%)	4,148 (22.5%)	2,160 (24.9%)	0.002	1,348 (28.5%)	3,526 (23.8%)	1,350 (28.5%)	0.001
Alcoholism	NTSR	19 (0.1%)	NTSR	0.003	NTSR	32 (0.2%)	NTSR	0.000
Aortic aneurysm	148 (1.7%)	274 (1.5%)	149 (1.7%)	0.001	88 (1.9%)	301 (2.0%)	89 (1.9%)	0.001
Revascularization procedure	20 (0.2%)	66 (0.4%)	20 (0.2%)	0.001	14 (0.3%)	70 (0.5%)	15 (0.3%)	0.004
Medications								
Thiazolidinedione	1,609 (18.6%)	2,161 (11.7%)	1,593 (18.4%)	0.005	964 (20.4%)	1,407 (9.5%)	987 (20.8%)	0.011
GLP-1 receptor agonist	173 (2.0%)	306 (1.7%)	177 (2.0%)	0.003	85 (1.8%)	182 (1.2%)	94 (2.0%)	0.014
Short-acting insulin	61 (0.7%)	159 (0.9%)	60 (0.7%)	0.002	40 (0.8%)	147 (1.0%)	42 (0.9%)	0.003
Anticholinergics	239 (2.8%)	407 (2.2%)	234 (2.7%)	0.003	183 (3.9%)	399 (2.7%)	176 (3.7%)	0.009
Statins	6,214 (71.7%)	12,315 (66.9%)	6,209 (71.7%)	0.000	2,985 (63.2%)	8,181 (55.3%)	3,007 (63.5%)	0.006
ACE inhibitors	3,830 (44.2%)	9,426 (51.2%)	3,819 (44.1%)	0.002	1,643 (34.8%)	5,982 (40.5%)	1,650 (34.8%)	0.001
ARB	2,701 (31.2%)	3,898 (21.2%)	2,694 (31.1%)	0.001	1,475 (31.2%)	3,163 (21.4%)	1,469 (31.0%)	0.004
Beta blockers	3,111 (35.9%)	6,897 (37.4%)	3,095 (35.7%)	0.004	1,877 (39.7%)	6,085 (41.2%)	1,871 (39.5%)	0.005
Calcium channel blockers	2,431 (28.1%)	4,863 (26.4%)	2,410 (27.8%)	0.005	1,324 (28.0%)	4,108 (27.8%)	1,309 (27.6%)	0.009
Other diuretics	115 (1.3%)	255 (1.4%)	116 (1.3%)	0.001	69 (1.5%)	228 (1.5%)	68 (1.4%)	0.003
Number metformin fills prior to pre-index date washout	6,590 (76.1%)	13,113 (71.2%)	6,587 (76.1%)	0.000	1,442 (30.5%)	3,218 (21.8%)	1,490 (31.4%)	0.020
Healthcare Utilization								
Lipid assessment	7,563 (87.3%)	15,085 (81.9%)	7,558 (87.3%)	0.000	3,924 (83.0%)	11,213 (75.8%)	3,931 (83.0%)	0.002
Mammography claim	2,094 (24.2%)	3,857 (20.9%)	2,103 (24.3%)	0.003	1,214 (25.7%)	3,370 (22.8%)	1,217 (25.7%)	0.000

Characteristic	Concurrent metformin users				Concurrent metformin non-users			
	DPP-4i N=8,665	Overall SU N=18,420	Subgroup Weighted SU N=8,660	Subgroup Weighted SMD	DPP-4i N=4,726	Overall SU N=14,786	Subgroup Weighted SU N=4,739	Subgroup Weighted SMD
Pap smear claim	611 (7.1%)	909 (4.9%)	607 (7.0%)	0.002	346 (7.3%)	815 (5.5%)	344 (7.3%)	0.002
Fecal occult blood test	772 (8.9%)	1,384 (7.5%)	783 (9.0%)	0.005	419 (8.9%)	1,139 (7.7%)	424 (8.9%)	0.003
Flu shot claim	4,712 (54.4%)	9,065 (49.2%)	4,714 (54.4%)	0.001	2,430 (51.4%)	6,835 (46.2%)	2,438 (51.4%)	0.000

Abbreviations: COPD=chronic obstructive pulmonary disease; DPP-4i=dipeptidyl peptidase-4 inhibitor; GI=gastrointestinal; GLP-1=glucagon-like peptide-1; IHD=ischemic heart disease; PVD=peripheral vascular disease; SD=standard deviation; SMD=standardized mean difference; SU=sulfonylurea; TIA=transient ischemic attack; UTI=urinary tract infection

Table 2.

Baseline characteristics for DPP-4i initiators, thiazolidinedione initiators, and subgroup weighted thiazolidinedione initiators (with subgroup-weighted standardized mean differences), stratified by concurrent metformin use and non-use.

Characteristic	Concurrent metformin users				Concurrent metformin non-users			
	DPP-4i N=15,141	Overall TZD N=5,983	Subgroup Weighted TZD N=15,162	Subgroup Weighted SMD	DPP-4i N=7,069	Overall TZD N=3,834	Subgroup Weighted TZD N=7,075	Subgroup Weighted SMD
Demographics								
Age, mean (SD)	71.7(3.75)	71.6(3.80)	71.6(3.80)	0.028	72.3(3.92)	72.2(3.99)	72.2(3.99)	0.032
Male sex	6,842 (45.2%)	2,955 (49.4%)	6,805 (44.9%)	0.006	2,725 (38.5%)	1,706 (44.5%)	2,736 (38.7%)	0.002
Race								
Other	2,310 (15.3%)	1,056 (17.7%)	2,320 (15.3%)	0.001	910 (12.9%)	534 (13.9%)	925 (13.1%)	0.006
White	11,533 (76.2%)	4,416 (73.8%)	11,555 (76.2%)	0.001	5,358 (75.8%)	2,866 (74.8%)	5,358 (75.7%)	0.002
Black	1,298 (8.6%)	511 (8.5%)	1,287 (8.5%)	0.003	801 (11.3%)	434 (11.3%)	792 (11.2%)	0.004
Comorbidities								
Acute myocardial infarction	108 (0.7%)	26 (0.4%)	112 (0.7%)	0.003	52 (0.7%)	15 (0.4%)	52 (0.7%)	0.001
Old myocardial infarction	309 (2.0%)	96 (1.6%)	327 (2.2%)	0.008	139 (2.0%)	57 (1.5%)	143 (2.0%)	0.004
Angina	475 (3.1%)	137 (2.3%)	479 (3.2%)	0.001	238 (3.4%)	131 (3.4%)	232 (3.3%)	0.005
Dyslipidemia	12,803 (84.6%)	4,881 (81.6%)	12,845 (84.7%)	0.005	5,694 (80.5%)	2,998 (78.2%)	5,687 (80.4%)	0.004
Hypertension	13,142 (86.8%)	5,030 (84.1%)	13,161 (86.8%)	0.000	5,976 (84.5%)	3,158 (82.4%)	5,981 (84.5%)	0.000
Stroke/TIA	561 (3.7%)	178 (3.0%)	572 (3.8%)	0.004	295 (4.2%)	140 (3.7%)	293 (4.1%)	0.002
Other acute/subacute IHD	204 (1.3%)	55 (0.9%)	204 (1.3%)	0.000	93 (1.3%)	46 (1.2%)	91 (1.3%)	0.002
Obesity	128 (0.8%)	47 (0.8%)	132 (0.9%)	0.003	80 (1.1%)	30 (0.8%)	89 (1.3%)	0.011
Diabetic nephropathy	385 (2.5%)	144 (2.4%)	382 (2.5%)	0.001	240 (3.4%)	110 (2.9%)	245 (3.5%)	0.004
Diabetic neuropathy	2,192 (14.5%)	749 (12.5%)	2,223 (14.7%)	0.005	879 (12.4%)	414 (10.8%)	875 (12.4%)	0.002
Diabetic retinopathy	1,980 (13.1%)	766 (12.8%)	1,981 (13.1%)	0.000	662 (9.4%)	384 (10.0%)	660 (9.3%)	0.001
Atherosclerosis	782 (5.2%)	225 (3.8%)	780 (5.1%)	0.001	417 (5.9%)	168 (4.4%)	413 (5.8%)	0.003
Bone fractures	499 (3.3%)	196 (3.3%)	516 (3.4%)	0.006	257 (3.6%)	130 (3.4%)	241 (3.4%)	0.013
COPD	1,531 (10.1%)	556 (9.3%)	1,563 (10.3%)	0.006	888 (12.6%)	447 (11.7%)	905 (12.8%)	0.007
Cancer (non-skin)	2,182 (14.4%)	785 (13.1%)	2,176 (14.4%)	0.002	1,114 (15.8%)	524 (13.7%)	1,108 (15.7%)	0.003
Chronic lung diseases	1,654 (10.9%)	545 (9.1%)	1,647 (10.9%)	0.002	880 (12.4%)	389 (10.1%)	883 (12.5%)	0.001
Connective tissue diseases	3,725 (24.6%)	1,269 (21.2%)	3,734 (24.6%)	0.001	1,975 (27.9%)	939 (24.5%)	1,964 (27.8%)	0.004
Dementia	314 (2.1%)	121 (2.0%)	322 (2.1%)	0.004	170 (2.4%)	110 (2.9%)	176 (2.5%)	0.005
Depression	1,626 (10.7%)	564 (9.4%)	1,623 (10.7%)	0.001	900 (12.7%)	408 (10.6%)	899 (12.7%)	0.001

Characteristic	Concurrent metformin users				Concurrent metformin non-users			
	DPP-4i N=15,141	Overall TZD N=5,983	Subgroup Weighted TZD N=15,162	Subgroup Weighted SMD	DPP-4i N=7,069	Overall TZD N=3,834	Subgroup Weighted TZD N=7,075	Subgroup Weighted SMD
Foot ulcers	916 (6.0%)	321 (5.4%)	935 (6.2%)	0.005	479 (6.8%)	252 (6.6%)	473 (6.7%)	0.004
Inflammatory GI diseases	72 (0.5%)	33 (0.6%)	74 (0.5%)	0.002	70 (1.0%)	42 (1.1%)	63 (0.9%)	0.010
Liver disease	805 (5.3%)	263 (4.4%)	838 (5.5%)	0.009	463 (6.5%)	215 (5.6%)	457 (6.5%)	0.004
Other chronic IHD	3,172 (20.9%)	1,042 (17.4%)	3,224 (21.3%)	0.008	1,587 (22.5%)	747 (19.5%)	1,601 (22.6%)	0.004
Other neurological disorders	2,033 (13.4%)	684 (11.4%)	2,059 (13.6%)	0.004	943 (13.3%)	454 (11.8%)	923 (13.0%)	0.009
Other ocular disorders	6,120 (40.4%)	2,229 (37.3%)	6,059 (40.0%)	0.009	2,749 (38.9%)	1,379 (36.0%)	2,738 (38.7%)	0.004
Other renal disorders	183 (1.2%)	62 (1.0%)	182 (1.2%)	0.001	212 (3.0%)	71 (1.9%)	211 (3.0%)	0.001
Pancreatitis	84 (0.6%)	31 (0.5%)	82 (0.5%)	0.002	58 (0.8%)	36 (0.9%)	64 (0.9%)	0.010
PVD (claudication)	1,256 (8.3%)	386 (6.5%)	1,280 (8.4%)	0.005	607 (8.6%)	301 (7.9%)	612 (8.7%)	0.002
Proteinuria	358 (2.4%)	133 (2.2%)	353 (2.3%)	0.002	163 (2.3%)	63 (1.6%)	172 (2.4%)	0.008
Tobacco use diagnosis	1,213 (8.0%)	361 (6.0%)	1,224 (8.1%)	0.002	646 (9.1%)	252 (6.6%)	658 (9.3%)	0.006
UTI/cystitis	2,413 (15.9%)	799 (13.4%)	2,430 (16.0%)	0.003	1,252 (17.7%)	574 (15.0%)	1,251 (17.7%)	0.001
Upper respiratory disorders	3,872 (25.6%)	1,390 (23.2%)	3,897 (25.7%)	0.003	1,922 (27.2%)	959 (25.0%)	1,897 (26.8%)	0.009
Alcoholism	12 (0.1%)	NTSR	12 (0.1%)	0.000	NTSR	NTSR	NTSR	0.002
Aortic aneurysm	246 (1.6%)	85 (1.4%)	254 (1.7%)	0.004	126 (1.8%)	61 (1.6%)	129 (1.8%)	0.003
Revascularization procedure	43 (0.3%)	NTSR	53 (0.3%)	0.011	32 (0.5%)	13 (0.3%)	34 (0.5%)	0.005
Medications								
Sulfonylurea	7,928 (52.4%)	3,529 (59.0%)	7,895 (52.1%)	0.006	3,172 (44.9%)	1,808 (47.2%)	3,190 (45.1%)	0.004
GLP-1 receptor agonist	369 (2.4%)	151 (2.5%)	391 (2.6%)	0.009	179 (2.5%)	97 (2.5%)	177 (2.5%)	0.002
Short-acting insulin	128 (0.8%)	50 (0.8%)	130 (0.9%)	0.001	79 (1.1%)	38 (1.0%)	74 (1.0%)	0.007
Anticholinergics	383 (2.5%)	121 (2.0%)	390 (2.6%)	0.003	228 (3.2%)	92 (2.4%)	244 (3.4%)	0.013
Statins	10,947 (72.3%)	4,168 (69.7%)	10,976 (72.4%)	0.002	4,567 (64.6%)	2,300 (60.0%)	4,594 (64.9%)	0.007
ACE inhibitors	7,450 (49.2%)	3,231 (54.0%)	7,485 (49.4%)	0.003	2,838 (40.1%)	1,693 (44.2%)	2,853 (40.3%)	0.004
ARB	4,479 (29.6%)	1,406 (23.5%)	4,481 (29.6%)	0.001	2,121 (30.0%)	916 (23.9%)	2,128 (30.1%)	0.002
Beta blockers	5,944 (39.3%)	2,084 (34.8%)	5,948 (39.2%)	0.001	2,961 (41.9%)	1,381 (36.0%)	2,982 (42.2%)	0.005
Calcium channel blockers	4,559 (30.1%)	1,668 (27.9%)	4,557 (30.1%)	0.001	2,090 (29.6%)	1,051 (27.4%)	2,104 (29.7%)	0.004
Other diuretics	233 (1.5%)	70 (1.2%)	237 (1.6%)	0.002	94 (1.3%)	53 (1.4%)	100 (1.4%)	0.007
Number metformin fills prior to pre-index date washout	12,431 (82.1%)	4,777 (79.8%)	12,422 (81.9%)	0.004	2,542 (36.0%)	1,136 (29.6%)	2,536 (35.8%)	0.002
Healthcare Utilization								
Lipid assessment	13,397 (88.5%)	5,125 (85.7%)	13,427 (88.6%)	0.002	5,920 (83.7%)	3,101 (80.9%)	5,942 (84.0%)	0.006
Mammography claim	3,696 (24.4%)	1,251 (20.9%)	3,739 (24.7%)	0.006	1,856 (26.3%)	870 (22.7%)	1,853 (26.2%)	0.002

Characteristic	Concurrent metformin users				Concurrent metformin non-users			
	DPP-4i N=15,141	Overall TZD N=5,983	Subgroup Weighted TZD N=15,162	Subgroup Weighted SMD	DPP-4i N=7,069	Overall TZD N=3,834	Subgroup Weighted TZD N=7,075	Subgroup Weighted SMD
Pap Smear claim	964 (6.4%)	362 (6.1%)	976 (6.4%)	0.003	451 (6.4%)	216 (5.6%)	454 (6.4%)	0.001
Fecal occult blood test	1,328 (8.8%)	490 (8.2%)	1,343 (8.9%)	0.003	622 (8.8%)	277 (7.2%)	636 (9.0%)	0.007
Flu shot claim	8,165 (53.9%)	2,989 (50.0%)	8,233 (54.3%)	0.008	3,706 (52.4%)	1,854 (48.4%)	3,721 (52.6%)	0.003

Abbreviations: COPD=chronic obstructive pulmonary disease; DPP-4i=dipeptidyl peptidase-4 inhibitor; GI=gastrointestinal; GLP-1=glucagon-like peptide-1; IHD=ischemic heart disease; PVD=peripheral vascular disease; SD=standard deviation; SMD=standardized mean difference; TIA=transient ischemic attack; TZD=thiazolidinedione; UTI=urinary tract infection

Table 3.

Comparison of subgroup-weighted, one-year outcome incidence after initiation of DPP-4i versus comparator drugs in the presence or absence of concurrent metformin use.

	Concurrent metformin users		Concurrent metformin non-users	
DPP-4i vs. sulfonylurea outcome	**Incidence per 100 patient-years† (95% CI)**	**ARD with DPP-4i vs. sulfonylurea (95% CI)**	**Incidence per 100 patient-years† (95% CI)**	**ARD with DPP-4i vs. sulfonylurea (95% CI)**
Composite outcome‡				
DPP-4i	3.7 (3.1 to 4.2)	−2.0 (−2.7 to −1.3)	3.4 (2.9 to 4.1)	−1.0 (−1.8 to −0.2)
Sulfonylurea	5.6 (5.2 to 6.1)		4.5 (4.0 to 5.0)	
All-cause mortality				
DPP-4i	2.9 (2.4 to 3.4)	−1.5 (−2.1 to −0.9)	2.6 (2.1 to 3.2)	−0.7 (−1.4 to 0.0)
Sulfonylurea	4.4 (4.0 to 4.8)		3.3 (2.9 to 3.7)	
Non-fatal MI				
DPP-4i	0.4 (0.2 to 0.6)	−0.5 (−0.8 to −0.3)	0.7 (0.5 to 1.1)	0.1 (−0.2 to 0.4)
Sulfonylurea	1.0 (0.8 to 1.2)		0.7 (0.5 to 0.8)	
Stroke				
DPP-4i	0.4 (0.3 to 0.6)	−0.1 (−0.3 to 0.1)	0.3 (0.1 to 0.5)	−0.5 (−0.7 to −0.2)
Sulfonylurea	0.5 (0.4 to 0.7)		0.8 (0.6 to 0.9)	
DPP-4i vs. thiazolidinedione outcome	**Incidence per 100 patient-years† (95% CI)**	**ARD with DPP-4i vs. thiazolidinedione (95% CI)**	**Incidence per 100 patient-years† (95% CI)**	**ARD with DPP-4i vs. thiazolidinedione (95% CI)**
Composite outcome‡				
DPP-4i	3.9 (3.5 to 4.3)	−0.6 (−1.5 to 0.2)	4.4 (3.9 to 5.0)	1.0 (0.0 to 2.0)
Thiazolidinedione	4.5 (3.8 to 5.2)		3.4 (2.7 to 4.2)	
All-cause mortality				
DPP-4i	2.9 (2.6 to 3.3)	−0.5 (−1.3 to 0.1)	3.3 (2.8 to 3.8)	0.8 (−0.0 to 1.7)
Thiazolidinedione	3.5 (2.9 to 4.1)		2.4 (1.8 to 3.1)	
Non-fatal MI				
DPP-4i	0.6 (0.5 to 0.8)	−0.1 (−0.4 to 0.2)	0.8 (0.6 to 1.1)	0.2 (−0.1 to 0.6)
Thiazolidinedione	0.7 (0.4 to 1.0)		0.6 (0.3 to 0.9)	
Stroke				
DPP-4i	0.5 (0.3 to 0.6)	−0.0 (−0.3 to 0.2)	0.7 (0.5 to 0.9)	0.0 (−0.4 to 0.5)
Thiazolidinedione	0.5 (0.3 to 0.8)		0.6 (0.3 to 1.0)	

Abbreviations: ARD=absolute rate difference; DPP-4i=dipeptidyl peptidase-4 inhibitor; MI=myocardial infarction

† Subgroup-weighted incidence

‡ Composite outcome includes all-cause mortality, non-fatal MI, and stroke

Table 4.

Analysis of interaction between concurrent metformin use/non-use and initiation of DPP-4i versus comparator drugs for subgroup-weighted one-year outcomes.

Outcome	Parameter estimate for interaction between metformin status and initiation drug	Interaction term p-value
DPP-4i vs. sulfonylurea		
Composite outcome[†]	−0.15 (−0.41 to 0.12)	0.290
All-cause mortality	−0.16 (−0.47 to 0.16)	0.334
Non-fatal MI	−0.92 (−1.60 to −0.24)	0.008
Stroke	0.87 (−0.02 to 1.77)	0.055
DPP-4i vs. thiazolidinedione		
Composite outcome[†]	−0.38 (−0.71 to −0.05)	0.024
All-cause mortality	−0.44 (−0.83 to −0.06)	0.023
Non-fatal MI	−0.41 (−1.15 to 0.33)	0.282
Stroke	−0.08 (−0.97 to 0.80)	0.863

Abbreviations: DPP-4i=dipeptidyl peptidase-4 inhibitor; MI=myocardial infarction

[†]Composite outcome includes all-cause mortality, non-fatal MI, and stroke