Calendar time as an instrumental variable in assessing the risk of heart failure with antihyperglycemic drugs

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Abstract

Objective: In recent years, second-line diabetes treatment with dipeptidyl peptidase-4 inhibitors (DPP-4i) increased with a corresponding decrease in thiazolidinediones (TZDs). Using hospitalization for heart failure (HF) as a positive control outcome, we explored the use of calendar time as an instrumental variable (IV) and compared this approach to an active comparator new-user study.

Methods: We identified DPP-4i or TZD initiators after a 6-month washout using Medicare claims 2006–2013. The IV was defined as a binary variable comparing initiators during October 2010 to December 2013 (postperiod) versus January 2008 to May 2010 (preperiod). We examined IV strength and estimated risk differences (RDs) for HF using Kaplan-Meier curves, which were compared with propensity score (PS)-weighted RD for DPP-4i versus TZD.

Results: The IV compared 22 696 initiators (78% DPP-4i) in the postperiod versus 20 283 initiators (38% DPP-4i) in the preperiod, resulting in 40% compliance. The active-comparator (PS-weighted) approach compared 26 198 DPP-4i and 18 842 TZD initiators. Covariate balance across IV levels was slightly better than across treatments (standardized difference, 3% vs 4.5%). The 1- and 2-year local average treatment effects of RD of HF per 100 patients in the “compliers” (95% confidence intervals) were −0.62 (−0.99 to −0.25) and −0.88 (−1.46 to −0.25). Corresponding PS-weighted results were −0.20 (−0.33 to −0.05) and −0.18 (−0.30 to 0.03).

Conclusion: Both approaches indicated lesser risk of HF hospitalizations among DPP-4i vs TZD initiators. The magnitude of the estimated effects may differ due to differences in the target populations and assumptions. Calendar time can be leveraged as an IV when market dynamics lead to profound changes in treatments.

KEYWORDS

calendar time, instrumental variables, pharmacoepidemiology

1 | INTRODUCTION

Antihyperglycemic drugs are critical components of diabetes management, accounting for approximately 12% of diabetes costs.^{1–3}

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While several new antidiabetic drugs were introduced in the market in the last decade, there also emerged safety concerns about thiazolidinediones (TZDs), an established class of antihyperglycemic drugs. In 2007, a meta-analysis raised concerns over the cardiovascular safety of rosiglitazone,⁴ after which it was pulled from the European market,⁵ and in September 2010, the Food and Drug

Administration (FDA) announced that its use would be severely restricted in the United States.⁶ Also in 2010, the FDA released a drug safety communication about the risk of bladder cancer with pioglitazone⁷ and in 2011 approved updates to the pioglitazone product labels to include this warning.⁸ According to a recent analysis,³ the dipeptidyl peptidase-4 (DPP-4i) class quickly gained significant market share and was the most commonly prescribed new drug class by 2012, but the use of TZDs decreased by 2012.

In observational studies, an active comparator balances the treatment cohorts with respect to measured and unmeasured confounders, thereby minimizing the potential for confounding by indication.⁹ Dipeptidyl peptidase-4 and TZD are both recommended as second-line antihyperglycemic drugs, with intermediate (DPP-4i) to high (TZD) efficacy, low risk of hypoglycemia,¹⁰ and comparable costs before the generic pioglitazone was introduced in August 2012.¹¹ The DPP-4i and TZD drugs are therefore expected to be in therapeutic equipoise in a population excluding anyone with clear contraindications.¹² The increased use of DPP-4i with a simultaneous decrease in TZD use over a short period also provides an opportunity to use calendar time as an instrumental variable (IV).¹³ Instrumental variable methods serve as a natural experiment to compare drugs in settings where substantial unmeasured confounding is expected.¹⁴⁻¹⁶ Common IV in pharmacoepidemiology includes provider preference, calendar time, distance to care, and geographic variation.¹⁷ Calendar time IV arises from secular trends in medication use. Such trends can be a result of effectiveness or safety releases, changes in physician preferences, formularies, or the introduction of new agents to the market. Calendar time IV has been previously used in several settings including studies of antidiabetic therapies on body mass index,¹⁸ colon cancer treatments on survival,¹³ antivirals in HIV patients,¹⁹ hormone replacement therapy, and myocardial infarction.²⁰

Our study setting is unique as there exist both an active comparator and also a potential calendar time IV arising from drug safety concerns. Using hospitalization for heart failure (HF) as a positive control outcome (increased HF risk with TZDs, not with DPP-4i drugs sitagliptin and alogliptin),²¹⁻²³ we first explored the use of calendar time as an IV. Next we compared this approach with an active comparator new-user study examining DPP-4i versus TZD in a sample of Medicare beneficiaries without prior HF.

2 | METHODS

We used a 20% random sample of the 2007–2013 Medicare claims data for this study. These data contain information about demographics, enrollment, inpatient, outpatient diagnoses, procedures, and prescription drugs for each enrollee.^{24,25}

From a population of Medicare beneficiaries aged >65 years, we identified new users of DPP-4i or TZD without the use of either drugs in the prior 6 months. Index date was defined as the date of the first prescription. Since TZDs are contraindicated in patients with existing HF,²⁶ we excluded patients with diagnoses of HF and related conditions (cardiomyopathy, arrhythmias, chronic kidney disease, edema, and loop diuretic use). We required the patients to have at least 6 months of continuous part D enrollment and at least 12 months

KEY POINTS

- In recent years, second-line treatment of patients with type 2 diabetes with dipeptidyl peptidase-4 inhibitors (DPP-4i) increased with a corresponding decrease in thiazolidinediones (TZDs). This crossover over a short period may provide an opportunity to use calendar time as an instrumental variable (IV). Using hospitalization for heart failure (HF) as a positive control outcome, we explored the use of calendar time as an IV and compared this approach to an active comparator new-user study comparing DPP versus TZD.
- The binary IV defined based on drug initiation patterns and the timing of safety signals compared initiators during October 2010 to December 2013 ("postperiod") versus January 2008 to May 2010 ("preperiod"), resulting in 40% compliance, which implies this is a strong IV. Using Kaplan-Meier methods, we estimated the 1- and 2-year risk differences for HF hospitalization using 2 approaches: (1) IV approach comparing postperiod versus preperiod and (2) active comparator approach comparing DPP-4i versus TZD initiators using propensity score weighting.
- Both approaches including many sensitivity analyses indicated lesser risk of HF hospitalizations among DPP-4i vs TZD initiators. The magnitude of the estimated effects may differ due to differences in the assumptions and target populations.
- Our results demonstrate that calendar time can be leveraged as an IV when market dynamics lead to profound changes in treatments over short periods.

parts A and B enrollment preindex. To ensure that patients were actually started on the drugs, we restricted our cohorts to patients with a second prescription for the same drug class dispensed within 6 months after the index date.

2.1 | Instrumental variable

An IV is an observed variable associated with the variation in exposure similar to randomized assignment.¹⁶ To be valid, an IV must be (1) associated with the treatment, (2) unrelated to patient characteristics, and (3) related to the outcome only through its association with the treatment. Additionally, to estimate the average treatment effect in the "compliers," the instrument should affect treatment deterministically in one direction (monotonicity assumption).¹⁶

We defined the IV as a binary variable ("postperiod" versus "preperiod") anchored around the time of the crossover of the drug initiation curves (June to September 2010), which was also the time when the FDA issued safety communications about TZDs. In our study, compliers are patients initiating TZD before the crossover and DPP-4i after the crossover. We identified an "optimal" IV by evaluating the percentage of compliers (the strength of the instrument's

effect on the received treatment).¹³ We examined the instrument in relation to IV assumptions using the proportion of compliers, partial *F* tests, measured covariates, and expert knowledge. In IV analyses, the approach of examining covariate balance by only looking at the standardized absolute mean differences (SAMDs) ignores the scaling factor and can be potentially misleading while evaluating confounding bias. Therefore, we evaluated covariate balance with the “actual treatment initiated” approach and IV approach by using both the SAMDs and bias components taking into account scaling of the IV as proposed by Jackson et al.²⁷ The binary measure of calendar time was decided before examining the effect estimates.

2.2 | Outcome

Heart failure hospitalization was defined as an inpatient claim with International Classification of Diseases, Ninth Revision, code 428.xx in the primary position.²⁸ Thiazolidinediones are known to increase HF risk,²¹ and while saxagliptin is suspected to be associated with an increased HF risk, other DPP-4i drugs (constituting >80% of our cohort, Table S1) are not.^{22,23,29} Heart failure hospitalization is therefore a positive control outcome in our study enabling the comparison of the analysis “comparing the actual treatments initiated” versus the “IV analysis comparing levels of the calendar time instrument.” Using an intent-to-treat (ITT) approach, patients were followed from the second prescription date until the earliest of HF hospitalization, death, end of enrollment, or 2 years after the index date.

2.3 | Confounding control and analysis

We used weighted Kaplan-Meier methods to estimate the 1- and 2-year risk differences (RDs) for HF hospitalization comparing (a) actual treatment received (DPP-4i vs TZD) and (b) IV approach (postperiod versus preperiod). Under the “treatment received” approach, we first estimated the propensity score (PS) for DPP-4i versus TZD³⁰ using logistic regression with baseline variables measured preinitiation. The year of initiation was not included in PS estimation because it was a suspected instrument strongly associated with the exposure but not with the outcome, and conditioning on such a variable could bias the

results and increase variance.³¹ We then assigned inverse probability of treatment weights (IPTW) of $1/PS$ to DPP-4i and $1/(1 - PS)$ to TZD and stabilized both groups by marginal prevalence of the treatment actually received.³² Using IPTW-weighted Kaplan-Meier curves, we estimated the RDs for HF hospitalization with treatment received as the strata variable and with a robust variance estimator.³³

The effect of the IV levels on HF hospitalization was observed by the IV estimates of 1- and 2-year RDs scaled by IV strength to estimate the local average treatment effect among compliers. In a secondary analysis, we generated covariate-adjusted IV estimates of the RD using weighted Kaplan-Meier methods analogous to the IPTW-weighted method and scaled this by IV strength.

These methods are appreciably different—IV estimates apply to the marginal patients while IPTW PS methods apply to the whole study population. Propensity score models used the full study population, and we performed sensitivity analyses in the reduced IV cohort to evaluate selection differences that may have been introduced based on IV exclusions.¹³ Next, we performed a sensitivity analysis restricting the study cohort to patients who initiated treatment between July 2007 and December 2011, with follow-up through December 2013. This approach excluded anyone who initiated therapy during or after January 2012, who would not have the potential for a 2-year follow-up before the end of the study). We also performed additional analyses with different definitions of the instrument to assess the effects of potential time trends in the outcome and effects of scaling by compliance percentage (Figures S2 and S3).

3 | RESULTS

The preferred treatments changed dramatically over the study period (Figure 1). The optimal binary IV compared the postperiod (October 2010 to December 2013, *N* = 22 696) with the preperiod (January 2008 to May 2010, *N* = 20 283). This definition excludes patients during June 2010 to September 2010 where the curves intersect. With this IV definition, the DPP-4i treatment rates were 78% and 38% in the postperiod and preperiod, respectively, and the strength

FIGURE 1 Initiation of dipeptidyl peptidase 4 inhibitors (DPP-4i) versus thiazolidinediones (TZD) across calendar time and the resultant definition of the instrumental variable (IV): Medicare claims data 2007–2013 [Colour figure can be viewed at wileyonlinelibrary.com]

of the IV (% compliers) was 40%. The partial *F* statistic assessing the association between the treatment and calendar time was 4596.7.

While the covariates were well balanced across DPP-4i versus TZD, the balance was slightly better across the levels of the IV as illustrated by the average SAMD of 4.5% vs 3.0%, respectively (Table 1). This indicates that the IV is independent of the measured risk factors of the outcome and potentially also unmeasured covariates. We also calculated the bias components to compare the covariate balance for the 2 analytic approaches (Table 1, last 2 columns). The bias component for the IV approach was relatively higher than the bias component with the “actual treatment initiated” approach for key variables like diabetic neuropathy, retinopathy, and baseline use of metformin and sulfonylureas, but the magnitude of the SAMD with both approaches was <10%.

In the full population comparing DPP-4i versus TZD, the crude incidence rate per 100 000 was 563 in DPP-4i and 676 in TZD initiators (Table 2). The 1- and 2-year risks for HF hospitalization were 0.5% and 1.2% for DPP-4i and 0.7% and 1.3% for TZD, respectively (Figure S1). In the reduced IV population, crude incidence rate per 100 000 person-years was 509 in the postperiod and 695 in the preperiod. The 1- and 2-year risks for HF hospitalization were 0.4% and 1.1% in the postperiod and 0.7% and 1.4% in the preperiod, respectively.

The crude RD was similar to the IPTW-weighted RD (Figure 2) obtained by comparing DPP-4i versus TZD, expected because of the balance of baseline covariates achieved by the use of an active comparator. The IV estimates of the RDs scaled by IV strength were consistent overall with the IPTW-weighted RDs indicating a protective effect with the DPP-4i but relatively less precise and farther from the null. The 2-year RD per 100 patients obtained using the IV analysis scaled by IV strength was -0.62 (-0.99 to -0.25) indicating that of the 1000 compliant patients treated with DPP-4i, 6 fewer patients would be expected to have an HF hospitalization during the first year relative to those with TZD. Covariate-adjusted IV estimates of the RD were similar (Figure 2, Table S2).

Sensitivity analyses in a population restricted to patients initiating on or before December 2011, analyses using IPTW weighting in the reduced IV population (Table S3), and analyses using different definitions of the IV to assess the effects of scaling and potential outcome time trends yielded similar results (Figures S2 and S3).

4 | DISCUSSION

This study compared the performance of 2 methods to estimate the effect of DPP-4i versus TZD initiation on the risk of HF hospitalization, a positive control outcome. The first method used an active comparator design using IPTW weighting, while the second method compared posttime versus pretime using calendar time as an IV and found lesser risk of HF hospitalization with DPP-4i.

The absolute 1-year risks of HF hospitalization in the sitagliptin and pioglitazone arms (together accounting for approximately 85% of our population; Table S1) were approximately 1% and 2%, respectively, in previous randomized trials.^{21,23} These trials found no increased risk with sitagliptin and 0.5% increased risk with

pioglitazone relative to placebo at 1 year; however, there are no data directly comparing DPP-4i with TZD. In our study, the claims-based HF definition had a high specificity but a low sensitivity,²⁸ which led to an underestimation of absolute HF risks and therefore also RDs for both the IPTW and IV methods. While we could have chosen to estimate relative risks, we chose to estimate RD because we were interested in an absolute measure of effect, which is more interpretable and relevant in our setting. Moreover, different IV methods used to derive relative measures require different additional assumptions like a special type of noncompliance (noncompliers are only those who do not take the treatment when assigned to the treatment) or about the homogeneity of risks within the levels of the treatment.^{16,34}

While the RDs from both approaches generally agreed, the IV estimates were less precise, and the magnitudes of the RDs differed because the 2 methods apply to different populations and are based on different assumptions. The IPTW-weighted RD is the average treatment effect in the entire population, while the scaled RD from the IV analysis is the average treatment effect in the 40% compliers from the reduced IV population. Scaling the RD involves dividing the RD by the IV strength of 40%. The weaker the instrument, the larger the scaled estimate gets relative to the unscaled RD, potentially magnifying any biases present in the unscaled RD.¹⁶ In a sensitivity analysis (Figure S2), we defined the instrument by a cut-point (before and after July 2010), which made this a weaker instrument (IV strength, 25%), and the scaled 1-year RD was -0.73 (-1.74 to 0.27), which has a larger magnitude than the main analysis, but in the same direction. In another analysis (Figure S3), we compared the periods with maximum separation (December 2011 to December 2012 versus June 2008 to June 2009). This definition led to a stronger IV (strength, 50%), and as expected, the scaled 1-year RD was closer to the unscaled estimate (-0.45 ; CI, -0.92 to 0.05). Thus, scaling could explain some of the differences in magnitude of the IV estimates of RDs compared with the IPTW-weighted RDs seen in the main analysis. We compared the characteristics of the compliers with that of the full population and found that the populations were generally similar with minor differences insufficient to explain our results (Table S4).

It is also important to critically assess IV assumptions. While we empirically observed that calendar time strongly affected the treatment initiation, the assumption of calendar time being unrelated to the outcome through other mechanisms could be potentially violated due to time trends in the outcome. However, no strong trends in HF hospitalizations were empirically observed in the population excluded from our study due to previous HF or other criteria (between 3.1% to 4.6% of the initiators were excluded each year during the study period due to a previous HF hospitalization). The literature reports reduction in the rates of HF hospitalization among Medicare beneficiaries due to several reasons including decreased smoking and increasing outpatient management.³⁵ The Hospital Readmissions Reduction Program started in late 2012 requires Centers for Medicare & Medicaid Services (CMS) to penalize hospitals with excess readmissions for certain conditions including HF, which may somewhat explain the decreasing trend in HF hospitalizations, but since this only affects a small proportion of our study period, this is not expected to meaningfully affect our results.³⁶

Assuming a decreasing trend in the rates of HF hospitalization during the study period, the estimates of RD are expected to be biased

TABLE 1 Covariate balance across levels of treatment initiated and the instrumental variable assessed by SAMD and Jackson Swanson bias components^a

	Patient Characteristics by Levels of the Instrument		Patient Characteristics by Actual Treatment Initiated		Covariate Balance using SAMD		Covariate Balance using Jackson Swanson Bias Components	
	Postperiod Oct 2013 to Dec 2013 (N = 22 696)	Preperiod Jan 2008 to May 2010 (N = 20 283)	DPP-4i (N = 26 198)	TZD (N = 18 842)	SAMD by Levels of the Instrument	SAMD by Actual Treatment Initiated	Difference in the Covariate Prevalence Across the Levels of the Instrument ^{*(1/0.40)}	Difference in the Covariate Prevalence Across the Actual Treatment Initiated
	%	%	%	%	%	%		
TZD	22.5	62.4	NA	NA	NA	NA	NA	NA
DPP-4i	77.5	37.6	NA	NA	NA	NA	NA	NA
Patient demographics at initiation								
Male	41.4	41.3	39.7	43.6	0.2	8	0.3	-3.9
Age								
66 to 75 years old	66.2	64.2	64.8	65.7	4.2	2	5.0	-0.9
76 to 85 years old	27.6	29.6	28.9	28.3	4.3	1.1	-5.0	0.6
86 years and above	6.1	6.2	6.4	5.9	0.3	1.8	-0.3	0.5
Race								
White	73.7	74	75.5	71.4	0.7	9.4	-0.8	4.1
Black	9.2	9.9	8.9	10.5	2.3	5.3	-1.7	-1.6
Other	17.1	16.1	15.6	18.2	2.7	6.8	2.5	-2.6
Baseline comorbidities ^b								
Diagnosis of acute myocardial infarction	0.8	0.7	0.8	0.5	1.5	3.9	0.2	0.3
Diagnosis of old myocardial infarction	2.2	1.8	2.2	1.6	2.9	4.5	1	0.6
Angina	3.2	3	3.5	2.6	1.2	5.3	0.5	0.9
Diagnosis of stroke or Transient Ischemic Attack (TIA)	4.8	3.9	4.7	4	4.5	3.2	2.2	0.7
Other acute and subacute forms of ischemic heart disease	1.4	1.2	1.6	1	1.7	4.6	0.5	0.6
Obesity diagnosis	0.9	0.8	1	0.6	1	3.8	0.3	0.4
Diabetic nephropathy	3	2.8	3	2.8	1.3	0.8	0.5	0.2
Diabetic neuropathy	15.2	12.8	15.3	12.7	7.1	7.4	6	2.6
Diabetic retinopathy	14.4	12.4	13.8	12.9	5.9	2.7	5	0.9
Bone fractures	4.4	3.6	4.1	3.9	3.8	0.6	2	0.2
Chronic obstructive pulmonary disease	11.2	10.2	11	10.4	3.2	1.9	2.5	0.6
Cancer (nonskin)	14.9	13	15.1	12.4	5.6	7.8	4.7	2.7
Dementia	4.9	4.7	4.9	4.6	0.9	1.2	0.5	0.3
Foot ulcers	7.1	5.9	7	5.8	4.9	4.7	3	1.2
Liver disease	5.3	4.3	5.2	4.3	4.4	4.5	2.5	0.9
Pancreatitis	0.8	0.7	0.8	0.7	0.8	0.5	0.3	0.1

(Continues)

TABLE 1 (Continued)

	Patient Characteristics by Levels of the Instrument		Patient Characteristics by Actual Treatment Initiated		Covariate Balance using SAMD		Covariate Balance using Jackson Swanson Bias Components	
	Postperiod Oct 2010 to Dec 2013 (N = 22 696)	Preperiod Jan 2008 to May 2010 (N = 20 283)	DPP-4i (N = 26 198)	TZD (N = 18 842)	SAMD by Levels of the Instrument	SAMD by Actual Treatment Initiated	Difference in the Covariate Prevalence Across the Levels of the Instrument ^a (1/0.40)	Difference in the Covariate Prevalence Across the Actual Treatment Initiated
Baseline medication use ^c								
Metformin	71.3	73.3	73.9	70.5	4.3	7.4	-5	3.4
Sulfonylureas	51.2	54.4	52	54.1	6.4	4.2	-8	-2.1
Glucagon-like peptide-1 agonists	1.7	1.8	1.8	1.6	0.4	1.2	-0.3	0.2
Long acting insulins	11.9	10.9	11.3	11.5	3	0.8	2.5	-0.2
Short acting insulin	4.3	4.2	4.1	4.4	0.5	1.2	0.3	-0.3
Statins	70.2	65.5	70.2	64.7	10.1	11.8	11.7	5.5
Angiotensin converting enzyme inhibitors	39.7	40.1	38.5	41.9	0.8	6.9	-1	-3.4
Angiotensin receptor blockers	16.6	15.6	17.3	14.4	2.5	7.8	2.5	2.9
Beta blockers	34.9	35.1	36.7	32.4	0.4	9	-0.5	4.3
Calcium channel blockers	27.1	25.3	27.1	25.2	4.1	4.3	4.5	1.9
Other diuretics	39.3	40.8	40.5	39.4	2.9	2.2	-3.7	1.1
Health care utilization ^b								
Blood tests	8.5	9.4	9.2	8.6	3.2	2.3	-2.3	0.6
Influenza vaccinations	55.9	52	56.2	51	7.8	10.4	9.7	5.2
Lipid panels	88.5	86.5	89.2	85.3	5.9	11.8	5	3.9
Mammogram	23	23.6	24.9	21.1	1.3	9	-1.5	3.8
Average SAMD					3	4.5	NA	NA

Abbreviations: DPP-4i, dipeptidyl peptidase-4 inhibitors; SAMD, standardized absolute mean difference; TZD, thiazolidinediones.

^aInstrumental variable definition anchored around the time of the Food and Drug Administration drug safety communications about thiazolidinediones and the crossing of the drug initiation curves. This definition excludes patients in the region where the curves intersect (June 2010 through September 2010) where the curves were close together (N = 2061, 4.5% of the total population of 45 040). Columns 6 and 7 present the SAMD by levels of the instrument and treatment, respectively. Columns 8 and 9 present the Jackson Swanson bias components across the levels of the instrument and treatment, respectively. Both the SAMD and bias components are means to evaluate covariate balance across levels of the instrument and levels of the treatment received. Bias components estimated based on the method described in Jackson et al (2015).

^bMeasured in the 12 months before initiation.

^cMeasured in the 6 months before initiation.

TABLE 2 Number of new users, heart failure hospitalizations, time on treatment, total person time, and incidence for comparisons of levels of the instrument and treatment initiated: Medicare claims data 2007–2013

Comparison	Level	Number of New Users	Events	Duration of Follow-up ^b in Years Interquartile Range (Median)	Total Person-years ^b	Incidence (per 100 000 Person-years)
Post vs Pre ^a	Post	22 696	146	1.36 (0.64–2.00)	28 661	509.40
	Pre	20 283	255	2.00 (2.00–2.00)	36 682	695.16
DPP-4i vs TZD	DPP-4i	26 198	210	2.00 (1.79–2.00)	37 252	563.73
	TZD	18 841	215	2.00 (1.68–2.00)	31 791	676.29

Abbreviations: DPP-4i, dipeptidyl peptidase–4 inhibitors; TZD, thiazolidinedione.

^aPost, October 2010 to December 2013; pre, January 2008 to May 2010.

^bUnder the first treatment carried forward/intent-to-treat analysis, patients were followed up from the second prescription of the initiated drug to earliest of the outcome occurrence, death, or 2 years after initiation without accounting for treatment changes during follow-up.

FIGURE 2 Comparison of risk differences (RDs) for heart failure hospitalization: Medicare claims data 2007–2013. Estimates of risk difference are based on risks per 100 patients estimated from Kaplan-Meier survival curves. The instrumental variable (IV) estimator is scaled by a compliance percentage of 40%. Adjusted estimates account for the variables presented in Table 1. IPTW, inverse probability of treatment weight; PS, propensity score [Colour figure can be viewed at wileyonlinelibrary.com]

in the direction of favoring DPP-4i relative to TZD. An increasing trend on the other hand is expected to bias the results against DPP-4i in favor of TZD. To minimize the effect of time trends, we conducted a sensitivity analysis using a dichotomous cut-point of calendar time (before and after July 2010) and estimated 1-year RD comparing the 12 months after versus before the cut-point. As described above, the RD observed was only slightly larger than the RD in the base-case

analysis but pointed in the same direction. The assumption that the IV is unrelated to patient characteristics is also not empirically verifiable, but it is upheld by the improvement in the covariate balance across post versus pre compared with the balance across DPP-4i versus TZD as indicated by the SAMD and bias components for the 2 approaches. The bias components for the IV approach were higher than the “actual treatment initiated” approach for key variables like

diabetic neuropathy, retinopathy, baseline use of metformin, and sulfonyleureas, indicating that not adjusting for these variables in the IV analyses would result in more bias than not adjusting them in the conventional PS-weighted active comparator analysis. However, the bias component method only gives an idea about the relative bias but not absolute bias.²⁷ In this study, the magnitude of the SAMD for both approaches was <10% for these variables, and our adjusted and unadjusted IV estimates are only slightly different indicating no significant concern for confounding by these variables in our main analysis. The assumption of monotonicity also seems to be reasonable in this study as it is unlikely that a patient would initiate DPP-4i in the preperiod while an identical patient would initiate TZD in the postperiod in spite of the warnings about TZD. Any impact of the generic pioglitazone in August 2012 on this study would be in the last year only and therefore unlikely to be a serious concern. There were no events that would preclude DPP-4i initiation in the preperiod from receiving DPP-4i in the postperiod, especially given the reports suggesting a lack of serious adverse events with these agents in the past few years.^{37,38}

Some additional caveats should be considered. Our ITT analysis approach could lead to exposure misclassification as it does not take into account treatment changes. However, the IV estimator is a measure of the association between the treatment assignment (i.e., treatment *intent*) and the outcome. Therefore, using a conceptually uniform ITT approach for the IPTW-weighted analysis comparing DPP-4i versus TZD initiation would facilitate direct comparison of the RDs obtained by the 2 methods. Finally, it could be argued that confounding exists in the DPP-4i versus TZD comparison by unmeasured factors like body mass index or smoking. However, body mass index is not likely to affect the choice of initiation of DPP-4i versus TZD in these patients, and chronic obstructive pulmonary disease was available as a proxy for smoking, which reduces the concern of confounding by these variables.³⁹

A key strength of our study was the identification of a calendar time IV that strongly affected the exposure, driven by the dynamics of the antihyperglycemic drug market. Time trends in the exposure also offer other study design options like secular trend analyses. Compared with a secular trend analysis that is more useful in forecasting future outcomes and generating hypotheses, using calendar time as a binary IV in this study enabled clear visualization of the measured patient characteristics by levels of the IV and enabled conditioning on any remaining imbalances while at the same time also checking if there is a trend in the outcome. These features make the IV method more intuitive while drawing conclusions about comparative performance of the treatments of interest.

It is often conservatively suggested to avoid IV methods when the assumptions are likely to be violated because relatively minor violations of the assumptions may lead to large biases.¹⁴ This can be particularly problematic when there is no valid comparison analytic method. In our setting, the use of a positive control outcome and observing consistent results with both IV and IPTW methods imply that both may be equally valid and supplement each other at the very least. Our results indicate that calendar time can be leveraged as a strong IV in settings where market dynamics lead to profound changes in preferred treatments.

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ETHICS STATEMENT

The authors state that no ethical approval was needed.

CONFLICT OF INTEREST

Dr Gokhale was a doctoral student at University of North Carolina during the conduct of this study. She is now a full-time employee of GlaxoSmithKline.

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Dr Mack is a full-time employee of Real-World and Late Phase Research, Quintiles, USA, and provides scientific consultation on studies for various pharmaceutical companies.

Dr Simpson has no conflicts of interest to report.

AUTHOR CONTRIBUTIONS

All authors participated in study conception and design and addressing reviewer comments. M.G., J.B., and T.S. participated in the acquisition of the data. M.G. did the analysis, and all authors contributed to the interpretation of the data. M.G. wrote the first draft of the manuscript. All authors reviewed and provided comments on the manuscript. M.G. is the guarantor of this work; M.G. and T.S. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.