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Postauthorization safety study of the DPP-4 inhibitor saxagliptin: a large-scale multinational family of cohort studies of five outcomes

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ABSTRACT

Objective To evaluate the risk of serious adverse events among patients with type 2 diabetes mellitus initiating saxagliptin compared with oral antidiabetic drugs (OADs) in classes other than dipeptidyl peptidase-4 (DPP-4) inhibitors.

Research design and methods Cohort studies using 2009–2014 data from two UK medical record data sources (Clinical Practice Research Datalink, The Health Improvement Network) and two USA claims-based data sources (HealthCore Integrated Research Database, Medicare). All eligible adult patients newly prescribed saxagliptin (n=110 740) and random samples of up to 10 matched initiators of non-DPP-4 inhibitor OADs within each data source were selected (n=913 384). Outcomes were hospitalized major adverse cardiovascular events (MACE), acute kidney injury (AKI), acute liver failure (ALF), infections, and severe hypersensitivity events, evaluated using diagnostic coding algorithms and medical records. Cox regression was used to determine HRs with 95% CIs for each outcome. Meta-analyses across data sources were performed for each outcome as feasible.

Results There were no increased incidence rates or risk of MACE, AKI, ALF, infection, or severe hypersensitivity reactions among saxagliptin initiators compared with other OAD initiators within any data source. Meta-analyses demonstrated a reduced risk of hospitalization/death from MACE (HR 0.91, 95% CI 0.85 to 0.97) and no increased risk of hospitalization for infection (HR 0.97, 95% CI 0.93 to 1.02) or AKI (HR 0.99, 95% CI 0.88 to 1.11) associated with saxagliptin initiation. ALF and hypersensitivity events were too rare to permit meta-analysis.

Conclusions Saxagliptin initiation was not associated with increased risk of MACE, infection, AKI, ALF, or severe hypersensitivity reactions in clinical practice settings.

Trial registration number NCT01086280, NCT01086293, NCT01086319, NCT01086306, and NCT01377935; Results.

Significance of this study

What is already known about this subject?

- Saxagliptin, a dipeptidyl peptidase-4 inhibitor, is an oral antidiabetic drug used in combination with diet and exercise to control hyperglycemia in adults with type 2 diabetes mellitus.
- Despite its widespread use in oral hypoglycemic therapy, few studies have evaluated the safety of saxagliptin in real-world settings.

What are the new findings?

- Saxagliptin initiation was not associated with significantly increased incidence rates or risk of major adverse cardiovascular events, infection, acute kidney injury, acute liver failure, or severe hypersensitivity reactions.

How might these results change the focus of research or clinical practice?

- These data provide no evidence for concern about an increase in risk of these outcomes from saxagliptin in real-world settings.

INTRODUCTION

Saxagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, is an oral antidiabetic drug (OAD) used in combination with diet and exercise to control hyperglycemia in adults with type 2 diabetes mellitus. This medication is approved for use as both monotherapy and combination therapy in the USA (approved July 2009) and as combination therapy in the European Union (approved October 2009).[1 2] Despite its widespread use in oral hypoglycemic therapy, few studies have evaluated the safety of saxagliptin in real-world settings. Since clinical trials are typically underpowered to detect uncommon, but potentially life-threatening, adverse reactions, postmarketing assessments are important to identify important medication-related toxicities in routine clinical practice.[3]

Prior to saxagliptin's approval in the USA and European Union, we designed an observational study within USA and UK practice settings to evaluate associations between saxagliptin and five outcomes of importance to patients with type 2 diabetes mellitus receiving OAD therapy, including major adverse cardiovascular events (MACE), acute liver failure (ALF), acute kidney injury (AKI), infections, and severe hypersensitivity reactions. After saxagliptin's approval, we prospectively collected data from 2009 to 2014 and compared the incidence rates and risk of each outcome between patients with type 2 diabetes mellitus who were new initiators of saxagliptin and those who were new initiators of OADs in classes other than DPP-4 inhibitors.

RESEARCH DESIGN AND METHODS

Data sources

We conducted cohort studies within two UK medical record data sources (Clinical Practice Research Datalink (CPRD), The Health Improvement Network (THIN)) and two USA claims-based data sources (HealthCore Integrated Research Database (HIRD), Medicare).[4] The study protocol and variables evaluated within each data source were previously described.[5]

Within the UK, CPRD contains electronic healthcare records for >15 million patients across 684 practices[6] and THIN contains medical records for >11 million patients across 550 practices.[7 8] This study analyzed the first 52 months of saxagliptin availability within the UK (2009–2014), using the March 2014 version of CPRD and the 1401 version of THIN. CPRD and THIN collect demographics, medical diagnoses and surgical procedures (recorded using Read codes), outpatient laboratory results, general practitioner-issued prescriptions, hospital admission and discharge dates, and dates and causes of death from Office for National Statistics' death certificate data.[9 10] Since some practices contribute to both CPRD and THIN, we identified and excluded patients in THIN who were also present within CPRD to avoid double-counting these individuals within analyses.[11]

Within the USA, HIRD is a commercial health insurance database serving 23.2 million members.[12–14] We analyzed HIRD data over the first 53 months of saxagliptin availability in the USA (2009–2013). Medicare is a federal health insurance program available to Americans aged ≥65 years and those under 65 years with certain disabilities or chronic health conditions.[15] We analyzed Medicare data over the first 41 months of saxagliptin availability in the USA (2009–2012) only, due to the 18-month time-lag in Medicare data availability for research. Both HIRD and Medicare contain demographic information, inpatient and outpatient medical diagnoses (recorded using International Classification of Diseases, Ninth Revision codes), surgical procedures (recorded with Current Procedural Terminology codes), and dispensed medications (recorded by National Drug Codes). The National Death Index was used to determine date and cause of death in both USA databases. To prevent double-counting patients concurrently enrolled in both USA data sources, HIRD data were only included for patients 18–64 years of age and enrollees were censored at age 65 years.

This study was approved by the UK Independent Scientific Advisory Committees for CPRD (Protocol 10_149RMn) and THIN (Protocol 11–039V), Quorum Review Institutional Review Board for HIRD, and Institutional Review Boards of the University of Pennsylvania and Rutgers University. A data use agreement was obtained from the Centers for Medicare and Medicaid Services.

Study patients

Patients were eligible if they were (1) ≥18 years, (2) newly initiated saxagliptin or an OAD in a class other than DPP-4 inhibitors (with or without additional OADs), and (3) enrolled in their data source for ≥180 days prior to initiation of saxagliptin or comparator OAD. The exposed cohort consisted of initiators of saxagliptin, prescribed as a single agent or a fixed-dose combination with metformin. The unexposed cohort consisted of initiators of OADs in classes other than DPP-4 inhibitors. Our rationale for not including initiators of other DPP-4 inhibitors in the comparator group was to ensure that we did not miss potentially important associations related to the DPP-4 class. Patients were excluded from primary analyses (though included in a sensitivity analysis) if they received insulin or glucagon-like peptide-1 (GLP-1) receptor agonists, since at the time of protocol design thorough investigations regarding the use of these therapies with saxagliptin had not been performed.

Within each data source, we selected all eligible saxagliptin initiators and a random sample of up to 10 eligible initiators of non-DPP-4 inhibitor OADs matched on age (within 5-year age groups), sex, and geographic region (ie, census region for USA data sources; country for UK data sources) to each saxagliptin initiator, to ensure sufficient sample sizes for subanalyses.

The index date was the date of first prescription/claim for saxagliptin or comparator OAD. The 180 days prior to this date represented the baseline period. Follow-up continued until study outcome, drug discontinuation (ie, no further drug claim or prescription within 30 days after the last days' supply), non-saxagliptin DPP-4 inhibitor initiation, or end of study, whichever occurred first.

Main study outcomes

The primary outcomes were (1) hospitalization with and/or death due to MACE, (2) hospitalization with ALF, (3) hospitalization for AKI, (4) hospitalization for infection, and (5) hospitalization for severe hypersensitivity reaction. We evaluated hospitalizations *for* AKI, infections, and hypersensitivity reactions because these conditions are frequently hospital-acquired. Evaluating hospitalizations *with* these conditions would leave open opportunities for diagnostic suspicion bias and include events that were not the main reason for hospitalization.[5]

End points were ascertained by diagnostic coding algorithms (see online supplementary tables S1-S11). MACE was defined by a hospital diagnosis of acute myocardial infarction (AMI), acute stroke, and/or death from cardiovascular causes (ie, AMI, acute stroke, congestive heart failure, dysrhythmia, sudden death, or coronary revascularization). Hospitalization with ALF was determined by inpatient diagnosis. Hospitalization for AKI was determined by inpatient AKI diagnosis plus at least one of the following within 7 days prior to admission: (1) emergency department AKI diagnosis, (2) outpatient AKI diagnosis, or (3) available serum creatinine result (within UK data) or claim for serum creatinine or serum chemistry panel including creatinine (within USA data). Hospitalization for infection was identified by inpatient infection diagnosis plus at least one of the following within 7 days prior to admission: (1) outpatient antimicrobial prescription/claim, (2) emergency department infection diagnosis, or (3) outpatient infection diagnosis. Hospitalization for severe hypersensitivity reaction was defined by (1) inpatient diagnosis for angioedema and/or generalized urticaria plus an emergency department or outpatient diagnosis of angioedema, urticaria, or rash within 7 days prior to admission; or (2) inpatient diagnosis for anaphylaxis, Stevens-Johnson syndrome, toxic epidermal necrolysis, or other severe skin reaction.

Within each data source, we sampled patients who met each diagnostic coding algorithm, requested records from these patients from general practitioners (in the UK) and hospitals (in the USA) to enable confirmation of endpoints, had clinicians with expertise in each outcome review these records to adjudicate events using criteria we previously published,[5] and calculated the positive predictive value (PPV) of the algorithms for confirmed events (see online supplementary table S12). We sought algorithms with >80% PPV to provide confidence that identified outcomes were true events. For any algorithm with <80% PPV within a data source (AKI within CPRD and THIN; infection within CPRD; ALF and severe hypersensitivity reactions within all data sources), we classified patients as having an event if (1) the outcome was confirmed by adjudication or (2) the patient met the algorithm but had no records available to confirm the event.

Data collection

Baseline data included demographic information, medical diagnoses, surgical procedures, and medications commonly prescribed in type 2 diabetes (table 1). We ascertained prior OAD use within the 180 days preceding the index date. Patients were considered to have 'switched to' the index drug if they were prescribed/dispensed an OAD within the 90 days prior to their index date but this drug was not prescribed/dispensed in the 90 days after that date. Patients were considered to have 'added on' their index drug to their OAD therapy if they continued to receive the same OADs within the 90 days prior to and 90 days after their index date.

Within the UK data sources, we collected the most recent hemoglobin A1c result prior to the index date, smoking status, and obesity (body mass index >30 kg/m^2). Within the USA data sources, we collected the number of claims for hemoglobin A1c tests recorded in the baseline period since laboratory results were not available for all enrollees within these data.

Statistical analysis

Within each data source, we compared characteristics between saxagliptin and comparator OAD initiators. Patients who had a study end point during the baseline period were excluded from analyses of that outcome. Unadjusted incidence rates of outcomes were calculated by cohort in each data source.

Because of the many potential confounders relative to the number of outcomes, we used propensity scores to control for confounding.[16] Propensity scores were developed within each data source using logistic regression, incorporating measured potential predictors of saxagliptin as independent variables and saxagliptin exposure as the dependent variable. We excluded patients from the saxagliptin cohort whose propensity score exceeded the maximum or minimum values in the comparator OAD cohort (trimmed the tails). All variables in tables 1 and 2 were included in propensity score models.

Cox regression was used to determine HRs with 95% CIs of outcomes in saxagliptin versus other OAD initiators, adjusting for propensity score, prior OAD therapy, quarter of observation, and geographic region. We adjusted for, rather than stratified or matched on, propensity score within multivariable models because (1) there were too few events within some propensity score strata to perform stratification and (2) unmatched saxagliptin initiators would have been excluded, reducing power to detect associations.

Meta-analyses of each outcome across data sources were performed as data permitted. The presence of heterogeneity in HRs across data sources was evaluated using the I^2 statistic.[17]

We performed sensitivity analyses to (1) evaluate outcomes when the cohorts were expanded to include patients prescribed/dispensed insulin or GLP-1 agonists and (2) examine the effect of unmeasured confounders on HRs of each outcome associated with saxagliptin use.[18] Details appear in online supplementary methods. Data were analyzed using SAS V.9.4.

RESULTS

Patient characteristics

We identified 110 740 eligible saxagliptin initiators and 913 384 eligible other OAD initiators (see online supplementary figure S1a-d). These patients' characteristics are presented in tables 1 (UK) and 2 (USA). Across the four data sources, the average follow-up ranged from 6.8 to 8.1 months among saxagliptin initiators and 5.6 to 7.0

Table 1 Demographic characteristics of patients with type 2 diabetes mellitus within the UK in the Clinical Practice Research Datalink (2009–2014) and The Health Improvement Network (2009–2014)

	Clinical Practice Research Datalink			The Health Improvement Network		
Characteristic*	**Saxagliptin (n=4181)**	**Other OAD (n=40 480)**	**Standardized difference§**	**Saxagliptin (n=873)**	**Other OAD (n=5564)**	**Standardized difference§**
Mean (SD) age, years†	54.65 (11.17)	53.77 (11.88)	0.0742	65.28 (13.11)	64.87 (13.10)	0.0313
Male sex†	2386 (57.1%)	22 852 (56.5%)	0.0124	517 (59.2%)	3234 (58.1%)	0.0223
UK country†						
England	2775 (66.4%)	27 347 (67.6%)	0.0252	496 (56.8%)	3507 (63.0%)	0.1271
Northern Ireland	190 (4.5%)	1843 (4.6%)	0.0004	46 (5.3%)	246 (4.4%)	0.0395
Scotland	429 (10.3%)	4235 (10.5%)	0.0066	165 (18.9%)	1184 (21.3%)	0.0594
Wales	787 (18.8%)	7055 (17.4%)	0.0362	166 (19.0%)	627 (11.3%)	0.2174
Other OAD initiated at index date						
Alpha-glucosidase inhibitors: acarbose	0 (0%)	75 (0.2%)	–	0 (0%)	15 (0.3%)	–
Biguanide: metformin	0 (0%)	27 151 (67.1%)	–	0 (0%)	3155 (56.7%)	–
Meglitinides	0 (0%)	122 (0.3%)	–	0 (0%)	16 (0.3%)	–
Nateglinide	0 (0%)	27 (0.1%)	–	–	–	–
Repaglinide	0 (0%)	95 (0.2%)	–	0 (0%)	16 (0.3%)	–
Sodium-glucose cotransporter 2: dapagliflozin	0 (0%)	50 (0.1%)	–	0 (0%)	29 (0.5%)	–
Sulfonylureas	0 (0%)	10 869 (26.9%)	–	0 (0%)	1907 (34.3%)	–
Glibenclamide (glyburide in US data sources)	0 (0%)	56 (0.1%)	–	0 (0%)	6 (0.1%)	–
Gliclazide	0 (0%)	9823 (24.3%)	–	0 (0%)	1696 (30.5%)	–
Glimepiride	0 (0%)	718 (1.8%)	–	0 (0%)	145 (2.6%)	–
Glipizide	0 (0%)	218 (0.5%)	–	0 (0%)	48 (0.9%)	–
Tolbutamide	0 (0%)	54 (0.1%)	–	0 (0%)	12 (0.2%)	–
Thiazolidinediones	0 (0%)	2213 (5.5%)	–	0 (0%)	442 (7.9%)	–
Pioglitazone	0 (0%)	2180 (5.4%)	–	0 (0%)	437 (7.9%)	–
Rosiglitazone	0 (0%)	33 (0.1%)	–	0 (0%)	5 (0.1%)	–
On glucagon-like peptide-1 receptor agonist	102 (2.4%)	821 (2.0%)	0.0278	16 (1.8%)	110 (2.0%)	0.0106
On insulin	304 (7.3%)	2813 (6.9%)	0.0125	67 (7.7%)	365 (6.6%)	0.0434
Hemoglobin A1c measurements						

Continued

Table 1 Continued

Characteristic*	Clinical Practice Research Datalink			The Health Improvement Network		
	Saxagliptin (n=4181)	Other OAD (n=40 480)	Standardized difference§	Saxagliptin (n=873)	Other OAD (n=5564)	Standardized difference§
Mean (SD)	8.801 (1.59)	8.646 (1.87)	0.0844	8.907 (1.62)	8.605 (1.81)	0.1689
Hemoglobin A1c>8%	2518 (60.2%)	16 166 (39.9%)	0.4144	513 (58.8%)	2324 (41.8%)	0.3449
Mean body mass index (SD)	32.23 (6.48)	31.59 (6.73)	0.0947	32.57 (6.47)	31.63 (6.42)	0.1468
Missing values	29 (0.7%)	1361 (3.4%)	0.1902	6 (0.7%)	104 (1.9%)	0.1054
Underweight (15–18.5 kg/m^2)	17 (0.4%)	246 (0.6%)	0.0283	1 (0.1%)	27 (0.5%)	0.0678
Normal (18.5–24.9 kg/m^2)	343 (8.2%)	4449 (11.0%)	0.0947	75 (8.6%)	633 (11.4%)	0.0930
Overweight (25.0–29.9 kg/m^2)	1171 (28.0%)	11 811 (29.2%)	0.0259	250 (28.6%)	1761 (31.6%)	0.0657
Obese (30–60 kg/m^2)	2621 (62.7%)	22 613 (55.9%)	0.1393	541 (62.0%)	3039 (54.6%)	0.1495
Smoking	2673 (63.9%)	24 390 (60.3%)	0.0759	529 (60.6%)	3450 (62.0%)	0.0290
Severity of type 2 diabetes mellitus (prior 180 days)						
Cerebrovascular disease	27 (0.6%)	262 (0.6%)	0.0002	7 (0.8%)	39 (0.7%)	0.0117
Coronary artery disease, congestive heart failure, ventricular tachycardia/ fibrillation	82 (2.0%)	561 (1.4%)	0.0449	12 (1.4%)	80 (1.4%)	0.0054
Diabetic coma	2 (0.0%)	33 (0.1%)	0.0133	0 (0%)	5 (0.1%)	–
Nephropathy	16 (0.4%)	72 (0.2%)	0.0387	6 (0.7%)	14 (0.3%)	0.0638
Neuropathy	39 (0.9%)	249 (0.6%)	0.0363	3 (0.3%)	37 (0.7%)	0.0454
Peripheral vascular disease	45 (1.1%)	373 (0.9%)	0.0156	7 (0.8%)	46 (0.8%)	0.0028
Retinopathy	247 (5.9%)	1331 (3.3%)	0.1253	40 (4.6%)	209 (3.8%)	0.0413
Unspecified additional diabetic complications	0 (0%)	6 (0.0%)	–	0 (0%)	3 (0.1%)	–
Medical comorbidities						
Allergic rhinitis/hay fever	398 (9.5%)	4343 (10.7%)	0.0401	59 (6.8%)	518 (9.3%)	0.0940
Asthma	711 (17.0%)	6652 (16.4%)	0.0153	137 (15.7%)	875 (15.7%)	0.0009
Chronic obstructive pulmonary disease/bronchitis	562 (13.4%)	3999 (9.9%)	0.1112	84 (9.6%)	557 (10.0%)	0.0131
Dermatological disorder						
Eczema	733 (17.5%)	6149 (15.2%)	0.0633	108 (12.4%)	743 (13.4%)	0.0294
Psoriasis/psoriatic arthritis	268 (6.4%)	2092 (5.2%)	0.0532	40 (4.6%)	283 (5.1%)	0.0235
Gastrointestinal disease						

Continued

Table 1 Continued

Characteristic*	Clinical Practice Research Datalink			The Health Improvement Network		
	Saxagliptin (n=4181)	Other OAD (n=40 480)	Standardized difference§	Saxagliptin (n=873)	Other OAD (n=5564)	Standardized difference§
Cirrhosis	16 (0.4%)	138 (0.3%)	0.0070	4 (0.5%)	18 (0.3%)	0.0216
Gallbladder disease	255 (6.1%)	2294 (5.7%)	0.0184	61 (7.0%)	325 (5.8%)	0.0468
Hemochromatosis	3 (0.1%)	64 (0.2%)	0.0255	1 (0.1%)	19 (0.3%)	0.0476
Hyperlipidemia	636 (15.2%)	4516 (11.2%)	0.1201	119 (13.6%)	634 (11.4%)	0.0676
Hypertension	2501 (59.8%)	19916 (49.2%)	0.2145	562 (64.4%)	3194 (57.4%)	0.1432
Infectious disease						
Hepatitis B virus infection	9 (0.2%)	65 (0.2%)	0.0126	1 (0.1%)	8 (0.1%)	0.0081
Hepatitis C virus infection	2 (0.0%)	49 (0.1%)	0.0252	0 (0%)	5 (0.1%)	–
Malignancy						
Hematological	36 (0.9%)	380 (0.9%)	0.0082	8 (0.9%)	54 (1.0%)	0.0056
Solid organ	1020 (24.4%)	9449 (23.3%)	0.0247	188 (21.5%)	1316 (23.7%)	0.0506
Obesity	692 (16.6%)	5951 (14.7%)	0.0510	130 (14.9%)	726 (13.0%)	0.0532
Rheumatoid arthritis	110 (2.6%)	881 (2.2%)	0.0297	9 (1.0%)	92 (1.7%)	0.0541
Medications						
Acetaminophen/paracetamol	1363 (32.6%)	11320 (28.0%)	0.1010	275 (31.5%)	1677 (30.1%)	0.0295
Antiasthmatic agents	826 (19.8%)	7326 (18.1%)	0.0423	161 (18.4%)	1017 (18.3%)	0.0042
Antibacterials	1566 (37.5%)	13997 (34.6%)	0.0600	279 (32.0%)	1710 (30.7%)	0.0264
Anticonvulsants	357 (8.5%)	3287 (8.1%)	0.0151	46 (5.3%)	292 (5.2%)	0.0009
Antifungals	111 (2.7%)	1066 (2.6%)	0.0013	27 (3.1%)	210 (3.8%)	0.0374
Antihistamines	306 (7.3%)	2914 (7.2%)	0.0046	72 (8.2%)	410 (7.4%)	0.0328
Antihyperlipidemic agents	3362 (80.4%)	22358 (55.2%)	0.5597	718 (82.2%)	3509 (63.1%)	0.4406
Antihypertensive agents						
ACE inhibitors	1921 (45.9%)	13740 (33.9%)	0.2469	405 (46.4%)	2151 (38.7%)	0.1569
Angiotensin receptor blockers	859 (20.5%)	5111 (12.6%)	0.2141	194 (22.2%)	829 (14.9%)	0.1892
Beta blockers	1090 (26.1%)	7928 (19.6%)	0.1550	246 (28.2%)	1393 (25.0%)	0.0712
Calcium channel blockers	1234 (29.5%)	9403 (23.2%)	0.1430	267 (30.6%)	1560 (28.0%)	0.0560
Loop diuretics	656 (15.7%)	4107 (10.1%)	0.1659	163 (18.7%)	654 (11.8%)	0.1935
Other antihypertensive agents	440 (10.5%)	2487 (6.1%)	0.1590	90 (10.3%)	393 (7.1%)	0.1154
Thiazide diuretics	808 (19.3%)	6110 (15.1%)	0.1123	220 (25.2%)	1180 (21.2%)	0.0947

Continued

Table 1 Continued

Characteristic*	Clinical Practice Research Datalink			The Health Improvement Network		
	Saxagliptin (n=4181)	Other OAD (n=40 480)	Standardized difference§	Saxagliptin (n=873)	Other OAD (n=5564)	Standardized difference§
Antivirals	36 (0.9%)	342 (0.8%)	0.0018	11 (1.3%)	40 (0.7%)	0.0547
Non-aspirin non-steroidal anti-inflammatory	474 (11.3%)	5042 (12.5%)	0.0346	106 (12.1%)	693 (12.5%)	0.0095
Other antiplatelet/ anticoagulant agents						
Aspirin	1590 (38.0%)	10625 (26.2%)	0.2543	375 (43.0%)	1827 (32.8%)	0.2097
Clopidogrel	229 (5.5%)	1421 (3.5%)	0.0950	42 (4.8%)	247 (4.4%)	0.0177
Low-molecular-weight heparin	10 (0.2%)	148 (0.4%)	0.0230	4 (0.5%)	22 (0.4%)	0.0096
Warfarin	241 (5.8%)	1979 (4.9%)	0.0390	66 (7.6%)	289 (5.2%)	0.0969
Other medications						
Allopurinol	183 (4.4%)	1396 (3.4%)	0.0479	54 (6.2%)	204 (3.7%)	0.1166
Antiarrhythmics	125 (3.0%)	1021 (2.5%)	0.0286	30 (3.4%)	181 (3.3%)	0.0102
Immune modulators/ immunosuppressants	56 (1.3%)	488 (1.2%)	0.0119	11 (1.3%)	71 (1.3%)	0.0014
Nitroglycerin	251 (6.0%)	1788 (4.4%)	0.0714	44 (5.0%)	284 (5.1%)	0.0029
Urinary antispasmodics	217 (5.2%)	1357 (3.4%)	0.0910	42 (4.8%)	199 (3.6%)	0.0616
Psychotropic agents						
Antidepressants	912 (21.8%)	8094 (20.0%)	0.0447	179 (20.5%)	1134 (20.4%)	0.0030
Antipsychotics	186 (4.4%)	1795 (4.4%)	0.0007	47 (5.4%)	269 (4.8%)	0.0249
Prior OAD therapy‡	3905 (93.4%)	12 855 (31.8%)	1.6523	814 (93.2%)	2228 (40.0%)	1.3665
Alpha-glucosidase inhibitors: acarbose	13 (0.3%)	47 (0.1%)	0.0422	3 (0.3%)	10 (0.2%)	0.0320
Biguanide: metformin	3384 (80.9%)	9857 (74.0%)	0.1677	681 (78.0%)	1800 (74.7%)	0.0774
Meglitinides	46 (1.1%)	97 (0.2%)	0.1056	7 (0.8%)	11 (0.2%)	0.0858
Nateglinide	7 (0.2%)	16 (0.0%)	0.0398	–	–	–
Repaglinide	40 (1.0%)	81 (0.2%)	0.0998	6 (0.7%)	7 (0.1%)	0.0882
Sodium-glucose cotransporter 2: dapagliflozin	1 (0.0%)	1 (0.0%)	0.0187	0 (0%)	2 (0.0%)	–
Sulfonylureas	1984 (47.5%)	4042 (10.0%)	0.9097	428 (49.0%)	661 (11.9%)	0.8822
Glibenclamide	14 (0.3%)	154 (0.4%)	0.0077	6 (0.7%)	38 (0.7%)	0.0004
Gliclazide	1689 (40.4%)	3176 (10.4%)	0.7354	362 (41.5%)	499 (12.9%)	0.6779

Continued

Table 1 Continued

Characteristic*	Clinical Practice Research Datalink			The Health Improvement Network		
	Saxagliptin (n=4181)	Other OAD (n=40 480)	Standardized difference§	Saxagliptin (n=873)	Other OAD (n=5564)	Standardized difference§
Glimepiride	212 (5.1%)	464 (1.2%)	0.2260	29 (3.3%)	79 (1.5%)	0.1223
Glipizide	52 (1.2%)	214 (0.5%)	0.0760	27 (3.1%)	35 (0.6%)	0.1825
Tolbutamide	27 (0.6%)	51 (0.1%)	0.0839	6 (0.7%)	14 (0.3%)	0.0637
Thiazolidinediones	614 (14.7%)	1527 (3.8%)	0.3839	145 (16.6%)	254 (4.6%)	0.3992
Pioglitazone	563 (13.5%)	1107 (2.9%)	0.3933	135 (15.5%)	167 (3.3%)	0.4286
Rosiglitazone	54 (1.3%)	427 (1.1%)	0.0219	12 (1.4%)	88 (1.6%)	0.0173

*Characteristics are presented as percentages unless otherwise indicated.
†Matching criteria for which a random sample (without replacement) of up to 10 new initiators of non-DPP-4 inhibitor OADs were selected for each saxagliptin initiator.
‡Defined as use of an OAD within the 180 days prior to the initiation of the index drug. Denominator adjusted to exclude the index drug.
§Standardized difference was calculated as the difference in mean (or proportion for binary variables) divided by the SD (pooled SD for continuous variables).
DPP-4, dipeptidyl peptidase-4; OAD, oral antidiabetic drug.

months among other OAD initiators. Saxagliptin initiators more commonly had hypertension and were more frequently prescribed/dispensed antihyperlipidemics, antihypertensives, and prior OAD therapy (metformin, sulfonylureas, and/or thiazolidinediones). Metformin initiators constituted the majority of the comparator OAD cohort.

The numbers of confirmed events following medical record review and PPVs of diagnostic coding algorithms varied by end point and data source (see online supplementary table S12).

Risk of MACE

There was no increased risk of MACE associated with saxagliptin initiation within any of the four data sources. Within Medicare, the incidence rate and risk of MACE was lower for saxagliptin than for other OAD initiators (HR 0.92, 95% CI, 0.86 to 0.98; table 3). Meta-analysis of results across the four data sources demonstrated a lower risk of MACE associated with saxagliptin initiation (HR 0.91, 95% CI 0.85 to 0.97; figure 1A).

Risk of ALF

There was no increased risk of ALF associated with saxagliptin initiation within each data source (table 3). Across the data sources, no saxagliptin initiators and only one comparator OAD initiator (within Medicare) developed ALF, and medical record review determined this was not drug-related. There were too few ALF events to permit meta-analysis.

Risk of AKI

There was no association between saxagliptin initiation and hospitalization for AKI across the data sources (table 3). Meta-analysis across the USA data sources demonstrated no increased risk of AKI with saxagliptin (HR 0.99, 95% CI, 0.88 to 1.11; figure 1B). The UK data sources were not included in the meta-analysis due to few events.

Risk of infection

Across the data sources, there was no association between saxagliptin initiation and hospitalization for infection (table 3). Meta-analysis of results within THIN, Medicare, and HIRD showed no increased risk of this outcome (HR 0.97, 95% CI 0.93 to 1.02; figure 1C). Data from CPRD were not included because the diagnostic coding algorithm had <80% PPV.

Risk of severe hypersensitivity reactions

There were no significant differences in incidence rates or risk of hospitalization for severe hypersensitivity reactions between saxagliptin and other OAD initiators within each data source (table 3). Across the data sources, only one saxagliptin initiator (within Medicare) had an event confirmed by medical record review. Due to the low number of events, we were unable to perform a meta-analysis.

Table 2 Demographic characteristics of patients with type 2 diabetes mellitus within the USA in Medicare (2009–2012) and the HealthCore Integrated Research Database (2009–2013)

	Medicare			HealthCore Integrated Reseach Database		
Characteristic*	**Saxagliptin (n=92 577)**	**Other OAD (n=7 40 328)**	**Standardized difference§**	**Saxagliptin (n=10 521)**	**Other OAD (n=1 00 343)**	**Standardized difference§**
Mean (SD) age, years†	70.46 (10.96)	69.86 (10.99)	0.0546	52.84 (8.39)	52.67 (8.48)	0.0196
Male sex†	39 916 (43.1%)	322 205 (43.5%)	0.0082	6303 (59.9%)	59 665 (59.5%)	0.0091
US census region†						
East North Central	11 453 (12.4%)	96 833 (13.1%)	0.0213	2245 (21.3%)	21 668 (21.6%)	0.0062
East South Central	8921 (9.6%)	71 154 (9.6%)	0.0009	1088 (10.3%)	10 425 (10.4%)	0.0016
Middle Atlantic	15 272 (16.5%)	114 684 (15.5%)	0.0274	897 (8.5%)	8396 (8.4%)	0.0057
Mountain	2952 (3.2%)	25 016 (3.4%)	0.0107	305 (2.9%)	2944 (2.9%)	0.0021
New England	2929 (3.2%)	22 293 (3.0%)	0.0088	600 (5.7%)	5863 (5.8%)	0.0060
Pacific	12 134 (13.1%)	97 652 (13.2%)	0.0025	1463 (13.9%)	14 209 (14.2%)	0.0073
South Atlantic	22 116 (23.9%)	177 647 (24.0%)	0.0025	3135 (29.8%)	29 474 (29.4%)	0.0093
West North Central	4896 (5.3%)	37 258 (5.0%)	0.0116	548 (5.2%)	5339 (5.3%)	0.0050
West South Central	11 900 (12.9%)	97 790 (13.2%)	0.0105	240 (2.3%)	2025 (2.0%)	0.0181
Other OAD initiated at index date						
Alpha-glucosidase inhibitors	0 (0%)	4334 (0.6%)	–	0 (0%)	343 (0.3%)	–
Acarbose	0 (0%)	4050 (0.5%)	–	0 (0%)	313 (0.3%)	–
Miglitol	0 (0%)	284 (0.0%)	–	0 (0%)	30 (0.0%)	–
Biguanide: metformin	0 (0%)	388 385 (52.5%)	–	0 (0%)	70 944 (70.7%)	–
Meglitinides	0 (0%)	17 007 (2.3%)	–	0 (0%)	802 (0.8%)	–
Nateglinide	0 (0%)	7652 (1.0%)	–	0 (0%)	374 (0.4%)	–
Repaglinide	0 (0%)	9355 (1.3%)	–	0 (0%)	428 (0.4%)	–
Sodium-glucose cotransporter 2: canagliflozin	0 (0%)	0 (0%)	–	0 (0%)	313 (0.3%)	–
Sulfonylureas	0 (0%)	258 866 (35.0%)	–	0 (0%)	21 196 (21.1%)	–
Chlorpropamide	0 (0%)	141 (0.0%)	–	0 (0%)	6 (0.0%)	–
Glimepiride	0 (0%)	85 584 (11.6%)	–	0 (0%)	7860 (7.8%)	–
Glipizide	0 (0%)	110 556 (14.9%)	–	0 (0%)	8098 (8.1%)	–
Glyburide (glibenclamide in UK data sources)	0 (0%)	61 794 (8.3%)	–	0 (0%)	5182 (5.2%)	–
Tolazamide	0 (0%)	725 (0.1%)	–	0 (0%)	48 (0.0%)	–
Tolbutamide	0 (0%)	66 (0.0%)	–	0 (0%)	2 (0.0%)	–
Thiazolidinediones	0 (0%)	71 254 (9.6%)	–	0 (0%)	6620 (6.6%)	–
Pioglitazone	0 (0%)	67 603 (9.1%)	–	0 (0%)	6295 (6.3%)	–
Rosiglitazone	0 (0%)	3651 (0.5%)	–	0 (0%)	325 (0.3%)	–
On glucagon-like peptide-1 receptor agonist	0 (0%)	0 (0%)	–	0 (0%)	0 (0%)	–
On insulin	14 716 (15.9%)	115 148 (15.6%)	0.0094	1073 (10.2%)	8469 (8.4%)	0.0605
Mean (SD) number of hemoglobin A1c measures	1.303 (0.88)	0.910 (0.86)	0.4572	1.148 (0.79)	0.771 (0.74)	0.5066
Severity of type 2 diabetes mellitus (prior 180 days)						
Cerebrovascular disease	9607 (10.4%)	77 376 (10.5%)	0.0024	242 (2.3%)	2288 (2.3%)	0.0013

Continued

Table 2 Continued

	Medicare			HealthCore Integrated Reseach Database		
Characteristic*	Saxagliptin (n=92 577)	Other OAD (n=7 40 328)	Standardized difference§	Saxagliptin (n=10 521)	Other OAD (n=1 00 343)	Standardized difference§
Coronary artery disease, congestive heart failure, ventricular tachycardia/ fibrillation	36 836 (39.8%)	279 939 (37.8%)	0.0406	1203 (11.4%)	10 791 (10.8%)	0.0217
Metabolic (ketoacidosis, hyperosmolar coma)	1199 (1.3%)	9220 (1.2%)	0.0044	80 (0.8%)	724 (0.7%)	0.0045
Nephropathy	18 387 (19.9%)	118 385 (16.0%)	0.1010	544 (5.2%)	3549 (3.5%)	0.0801
Neuropathy	20 973 (22.7%)	138 634 (18.7%)	0.0971	884 (8.4%)	6599 (6.6%)	0.0694
Peripheral vascular disease	16 822 (18.2%)	122 379 (16.5%)	0.0433	410 (3.9%)	3266 (3.3%)	0.0346
Retinopathy	12 102 (13.1%)	77 603 (10.5%)	0.0804	539 (5.1%)	3665 (3.7%)	0.0718
Unspecified additional diabetic complications	7123 (7.7%)	51 544 (7.0%)	0.0281	407 (3.9%)	2714 (2.7%)	0.0653
Medical comorbidities						
Allergic rhinitis/hay fever	6430 (6.9%)	41 153 (5.6%)	0.0573	542 (5.2%)	4623 (4.6%)	0.0253
Asthma	7001 (7.6%)	57 683 (7.8%)	0.0086	407 (3.9%)	4300 (4.3%)	0.0211
Chronic obstructive pulmonary disease/ bronchitis	11 171 (12.1%)	97 901 (13.2%)	0.0348	286 (2.7%)	2949 (2.9%)	0.0133
Dermatological disorders						
Eczema	3240 (3.5%)	22 611 (3.1%)	0.0250	225 (2.1%)	1916 (1.9%)	0.0163
Psoriasis/psoriatic arthritis	877 (0.9%)	6808 (0.9%)	0.0029	96 (0.9%)	887 (0.9%)	0.0030
Gastrointestinal disease						
Cirrhosis	686 (0.7%)	6014 (0.8%)	0.0081	32 (0.3%)	360 (0.4%)	0.0095
Gallbladder disease	1953 (2.1%)	16 763 (2.3%)	0.0106	111 (1.1%)	1137 (1.1%)	0.0075
Hemochromatosis	200 (0.2%)	1422 (0.2%)	0.0053	17 (0.2%)	164 (0.2%)	0.0005
Hyperlipidemia	71 221 (76.9%)	492 578 (66.5%)	0.2324	6550 (62.3%)	48 349 (48.2%)	0.2859
Hypertension	78 403 (84.7%)	577 668 (78.0%)	0.1717	6397 (60.8%)	50 751 (50.6%)	0.2069
Infections						
Hepatitis B virus infection	258 (0.3%)	1646 (0.2%)	0.0113	20 (0.2%)	134 (0.1%)	0.0141
Hepatitis C virus infection	725 (0.8%)	6826 (0.9%)	0.0151	56 (0.5%)	482 (0.5%)	0.0073
HIV	220 (0.2%)	2722 (0.4%)	0.0237	8 (0.1%)	172 (0.2%)	0.0271
Malignancy						
Hematological	1157 (1.2%)	10 146 (1.4%)	0.0106	63 (0.6%)	574 (0.6%)	0.0035
Solid organ	7837 (8.5%)	63 813 (8.6%)	0.0055	339 (3.2%)	3174 (3.2%)	0.0034
Obesity	10 711 (11.6%)	84 346 (11.4%)	0.0055	1006 (9.6%)	9899 (9.9%)	0.0102
Rheumatoid arthritis	2538 (2.7%)	18 429 (2.5%)	0.0158	90 (0.9%)	843 (0.8%)	0.0017
Medications						
Acetaminophen/ paracetamol	24 456 (26.4%)	1 94 424 (26.3%)	0.0035	2091 (19.9%)	19 897 (19.8%)	0.0011
Antiasthmatic agents	12 734 (13.8%)	92 459 (12.5%)	0.0375	836 (7.9%)	7720 (7.7%)	0.0094
Antibacterials	35 628 (38.5%)	257 225 (34.7%)	0.0777	3286 (31.2%)	29 277 (29.2%)	0.0448
Anticonvulsants	4707 (5.1%)	41 871 (5.7%)	0.0253	768 (7.3%)	7682 (7.7%)	0.0135
Antifungals	9132 (9.9%)	60 580 (8.2%)	0.0587	735 (7.0%)	5858 (5.8%)	0.0469
Antihistamines	9142 (9.9%)	61 223 (8.3%)	0.0559	645 (6.1%)	5406 (5.4%)	0.0319

Continued

Table 2 Continued

Characteristic*	Medicare			HealthCore Integrated Reseach Database		
	Saxagliptin (n=92 577)	Other OAD (n=7 40 328)	Standardized difference§	Saxagliptin (n=10 521)	Other OAD (n=1 00 343)	Standardized difference§
Antihyperlipidemic agents	59 126 (63.9%)	375 758 (50.8%)	0.2674	5233 (49.7%)	35 934 (35.8%)	0.2843
Antihypertensive agents						
ACE inhibitors	38 296 (41.4%)	278 503 (37.6%)	0.0767	3736 (35.5%)	27 518 (27.4%)	0.1748
Angiotensin receptor blockers	25 262 (27.3%)	133 659 (18.1%)	0.2219	2034 (19.3%)	13 433 (13.4%)	0.1613
Beta blockers	38 938 (42.1%)	268 421 (36.3%)	0.1191	2219 (21.1%)	18 338 (18.3%)	0.0709
Calcium channel blockers	28 176 (30.4%)	194 430 (26.3%)	0.0927	1670 (15.9%)	13 557 (13.5%)	0.0668
Loop diuretics	19 448 (21.0%)	131 150 (17.7%)	0.0834	524 (5.0%)	4726 (4.7%)	0.0126
Other antihypertensive agents	10 023 (10.8%)	65 686 (8.9%)	0.0656	474 (4.5%)	3840 (3.8%)	0.0340
Thiazide diuretics	18 813 (20.3%)	113 540 (15.3%)	0.1305	1846 (17.5%)	14 470 (14.4%)	0.0854
Antivirals	2005 (2.2%)	15 077 (2.0%)	0.0090	197 (1.9%)	2468 (2.5%)	0.0403
Non-aspirin non-steroidal anti-inflammatory	15 506 (16.7%)	109 437 (14.8%)	0.0540	1488 (14.1%)	13 098 (13.1%)	0.0318
Other antiplatelet/ anticoagulant agents						
Aspirin	644 (0.7%)	4504 (0.6%)	0.0108	16 (0.2%)	142 (0.1%)	0.0028
Clopidogrel	11 150 (12.0%)	69 439 (9.4%)	0.0862	363 (3.5%)	3035 (3.0%)	0.0240
Low-molecular-weight heparin	372 (0.4%)	3889 (0.5%)	0.0182	32 (0.3%)	288 (0.3%)	0.0032
Warfarin	6459 (7.0%)	51 316 (6.9%)	0.0018	203 (1.9%)	1652 (1.6%)	0.0214
Other medications						
Allopurinol	4924 (5.3%)	31 821 (4.3%)	0.0477	270 (2.6%)	2408 (2.4%)	0.0107
Antiarrhythmics	11 895 (12.8%)	88 324 (11.9%)	0.0279	489 (4.6%)	4407 (4.4%)	0.0123
Immune modulators/ immunosuppressants	3986 (4.3%)	29 604 (4.0%)	0.0154	223 (2.1%)	2400 (2.4%)	0.0183
Nitroglycerin	3995 (4.3%)	27 908 (3.8%)	0.0277	137 (1.3%)	1241 (1.2%)	0.0058
Urinary antispasmodics	4692 (5.1%)	32 809 (4.4%)	0.0299	112 (1.1%)	1185 (1.2%)	0.0110
Psychotropic agents						
Antidepressants	24 264 (26.2%)	186 970 (25.3%)	0.0218	1992 (18.9%)	18 828 (18.8%)	0.0043
Antipsychotics	6305 (6.8%)	54 109 (7.3%)	0.0195	222 (2.1%)	2197 (2.2%)	0.0055
Prior OAD therapy‡	68 160 (73.6%)	273 289 (36.9%)	0.7944	6957 (66.1%)	21 797 (21.7%)	1.0004
Alpha-glucosidase inhibitors	715 (0.8%)	1988 (0.3%)	0.0701	38 (0.4%)	118 (0.1%)	0.0499
Acarbose	636 (0.7%)	1730 (0.2%)	0.0668	35 (0.3%)	108 (0.1%)	0.0479
Miglitol	84 (0.1%)	260 (0.0%)	0.0222	4 (0.0%)	10 (0.0%)	0.0181
Biguanide: metformin	46 101 (49.8%)	1 40 212 (39.8%)	0.2013	5500 (52.3%)	12 578 (42.8%)	0.1909
Meglitinides	2430 (2.6%)	7708 (1.0%)	0.1183	140 (1.3%)	375 (0.4%)	0.1042
Nateglinide	1235 (1.3%)	3467 (0.5%)	0.0911	75 (0.7%)	182 (0.2%)	0.0796
Repaglinide	1231 (1.3%)	4286 (0.6%)	0.0764	67 (0.6%)	193 (0.2%)	0.0691
Sodium-glucose cotransporter 2: canagliflozin	–	–	–	5 (0.0%)	10 (0.0%)	0.0221
Sulfonylureas	36 848 (39.8%)	127 737 (17.3%)	0.5157	2874 (27.3%)	8168 (8.1%)	0.5187
Chlorpropamide	21 (0.0%)	221 (0.0%)	0.0044	1 (0.0%)	3 (0.0%)	0.0082

Continued

Table 2 Continued

Characteristic*	Medicare			HealthCore Integrated Reseach Database		
	Saxagliptin (n=92 577)	Other OAD (n=7 40 328)	Standardized difference§	Saxagliptin (n=10 521)	Other OAD (n=1 00 343)	Standardized difference§
Glimepiride	14 315 (15.5%)	35 805 (5.5%)	0.3309	1262 (12.0%)	2759 (3.0%)	0.3475
Glipizide	15 451 (16.7%)	56 241 (8.9%)	0.2338	1139 (10.8%)	3591 (3.9%)	0.2679
Glyburide	8116 (8.8%)	36 892 (5.4%)	0.1299	526 (5.0%)	1863 (2.0%)	0.1666
Tolazamide	3 (0.0%)	72 (0.0%)	0.0081	0 (0%)	10 (0.0%)	–
Tolbutamide	12 (0.0%)	54 (0.0%)	0.0056	1 (0.0%)	1 (0.0%)	0.0117
Thiazolidinediones	18 258 (19.7%)	54 840 (7.4%)	0.3656	1376 (13.1%)	4832 (4.8%)	0.2926
Pioglitazone	16 698 (18.0%)	45 435 (6.8%)	0.3475	1260 (12.0%)	4071 (4.3%)	0.2822
Rosiglitazone	1762 (1.9%)	9661 (1.3%)	0.0471	123 (1.2%)	785 (0.8%)	0.0391

*Characteristics are presented as percentages unless otherwise indicated.
†Matching criteria for which a random sample (without replacement) of up to 10 new initiators of non-DPP-4 inhibitor OADs were selected for each saxagliptin initiator.
‡Defined as use of an OAD within the 180 days prior to the initiation of the index drug. Denominator adjusted to exclude the index drug.
§Standardized difference was calculated as the difference in mean (or proportion for binary variables) divided by the SD (pooled SD for continuous variables).
DPP-4, dipeptidyl peptidase-4; OAD, oral antidiabetic drug.

Sensitivity analyses

When the cohorts were expanded to include patients who were prescribed/dispensed insulin and/or a GLP-1 agonist, there was no increased risk of any outcome within each data source (see online supplementary table S13). Across all data sources, sensitivity analyses to determine the potential impact of unmeasured confounders determined that the HRs for each outcome were not sensitive to unmeasured confounding (see onlinesupplementary table S14).

CONCLUSIONS

This very large family of cohort studies of two UK healthcare record data sources and two USA claims-based data sources (analyzed individually and combined via meta-analyses) found no increases in incidence rates or risk of hospitalization with or death due to MACE, hospitalization with ALF, or hospitalization for AKI, infection, or severe hypersensitivity reaction among new initiators of saxagliptin compared with new initiators of OADs in non-DPP-4 inhibitor classes.

Consistent with previously published studies,[19–25] we found no evidence of increased risk of MACE associated with saxagliptin initiation. A meta-analysis of 53 clinical trials for DPP-4 inhibitors found a reduced risk of MACE among patients prescribed DPP-4 inhibitors compared with those prescribed placebo or comparator therapies.[19] Similarly, the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 trial found that saxagliptin use was not associated with a higher risk of AMI, ischemic stroke, or cardiovascular death.[23] Our findings provide further evidence that saxagliptin is not associated with an increased risk of MACE in practice settings.

Post hoc analyses of clinical trials data have suggested no increased risk of acute liver injury with saxagliptin.[25] We observed no association between saxagliptin initiation and hospitalization with ALF. Notably, across the four data sources, we observed no ALF events among saxagliptin initiators and only one event among comparator OAD initiators.

Consistent with prior clinical trials,[26 27] this study demonstrated no association between saxagliptin initiation and hospitalization for AKI, confirming the renal safety of saxagliptin in real-world settings.

Our finding of no association between saxagliptin initiation and infection is consistent with the overall low incidence rates and risk of infection among DPP-4 inhibitors observed in clinical trials.[25 28] A pooled analysis of 20 randomized trials of saxagliptin, prescribed as a monotherapy or add-on therapy, found similar incidence rates of infection between saxagliptin users (24.2 per 100 patient-years) and the control groups (21.7 per 100 patient-years).[25] A meta-analysis of 30 randomized trials comparing vildagliptin with placebo also found no increased risk of infections.[28] However, one meta-analysis of randomized trials of DPP-4 inhibitors (sitagliptin, vildagliptin, saxagliptin) observed an increased risk of nasopharyngitis (risk ratio 1.2, 95% CI 1.0 to 1.4) and urinary tract infections (risk ratio 1.5, 95% CI 1.0 to 2.2) associated with DPP-4 inhibitor use.[29]

Our findings demonstrating no increased risk of hospitalizations for severe hypersensitivity reactions among saxagliptin initiators are in contrast with prior clinical trials analyses.[25 30] In one pooled analysis, urticaria and facial edema occurred more commonly

Table 3 Incidence rates and HRs of outcomes, by data source

Outcome, by data source	Saxagliptin initiators				Other OAD initiators				
	Users (n)	Person-years	Events (n)	Rate of events per 1000 person-years (95% CI)	Users (n)	Person-years	Events (n)	Rate of events per 1000 person-years (95% CI)	Adjusted HR* (95% CI)
Major cardiovascular event									
Medicare	70 271	39 300.8	1030	26.2 (24.6 to 27.9)	562 159	308 101.7	8945	29.0 (28.4 to 29.6)	0.92 (0.86 to 0.98)
HIRD	9219	5988.1	45	7.5 (5.5 to 10.1)	89 538	41 694.0	362	8.7 (7.8 to 9.6)	0.86 (0.62 to 1.20)
CPRD	3769	2551.4	13	5.1 (2.7 to 8.7)	35 916	20 245.3	145	7.2 (6.0 to 8.4)	0.63 (0.35 to 1.16)
THIN (excluding CPRD)	785	524.3	5	9.5 (3.1 to 22.3)	4873	2850.8	21	7.4 (4.6 to 11.3)	0.99 (0.34 to 2.87)
Acute liver failure									
Medicare†	72 831	41 011.4	28	0.7 (0.5 to 1.0)	72 831	37 260.1	40	1.1 (0.8 to 1.5)	0.72 (0.42 to 1.25)
HIRD†	9265	6059.8	2	0.3 (0.04 to 1.2)	90 174	42 230.7	6	0.1 (0.05 to 0.3)	2.97 (0.49 to 18.11)‡
CPRD†	3794	2581.4	0	0.0 (0.0 to 1.2)	36 196	20 549.8	0	0.0 (0.0 to 0.1)	–
THIN (excluding CPRD)†	791	531.0	0	0.0 (0.0 to 5.6)	4913	2879.5	0	0.0 (0.0 to 1.0)	–
Acute kidney injury									
Medicare	61 888	34 597.7	334	9.7 (8.6 to 10.7)	519 259	289 326.5	2708	9.4 (9.0 to 9.7)	0.99 (0.88 to 1.11)
HIRD	8894	5819.5	4	0.7 (0.2 to 1.8)	87 770	40 979.4	26	0.6 (0.4 to 0.9)	0.88 (0.29 to 2.74)
CPRD†	2972	1947.4	0	0.0 (0.0 to 1.5)	32 798	18 369.1	7	0.4 (0.2 to 0.8)	–
THIN (excluding CPRD)†	602	412.8	0	0.0 (0.0 to 7.3)	4327	2522.3	2	0.8 (0.10 to 2.9)	–
Infection									
Medicare	74 263	41 012.6	2280	55.6 (53.3 to 57.9)	577 572	314 496.9	17 840	56.7 (55.9 to 57.6)	0.97 (0.92 to 1.01)
HIRD	9300	6047.8	84	13.9 (11.1 to 17.2)	89 485	41 773.4	552	13.2 (12.1 to 14.4)	1.07 (0.83 to 1.37)
CPRD†	3714	2456.9	74	30.1 (23.7 to 37.8)	35 417	19 687.2	661	33.6 (31.1 to 36.2)	0.81 (0.63 to 1.06)
THIN (excluding CPRD)	780	508.9	2	3.9 (0.5 to 14.2)	4834	2785.5	18	6.5 (3.8 to 10.2)	0.64 (0.13 to 3.16)
Hypersensitivity									
Medicare†	77 857	43 764.4	75	1.7 (1.3 to 2.1)	624 074	342 886.0	702	2.0 (1.9 to 2.2)	0.80 (0.62 to 1.02)
HIRD†	9439	6162.2	4	0.6 (0.2 to 1.7)	91 814	42 887.8	72	1.7 (1.3 to 2.1)	0.48 (0.17 to 1.38)
CPRD†	3795	2581.5	2	0.8 (0.09 to 2.8)	36 245	20 558.8	13	0.6 (0.3 to 1.1)	1.80 (0.31 to 10.28)‡
THIN (excluding CPRD)†	792	531.6	0	0.0 (0.0 to 5.6)	4921	2884.2	0	0.0 (0.0 to 1.0)	–

*Adjusted for prior OAD therapy, quarter of observation, and geographic region unless otherwise noted.
†A validated algorithm was unable to be determined, so, conservatively, we included all electronically identified outcomes that were either confirmed by medical record review or had unobtained charts as events.
‡Since there were not enough events to run the fully adjusted model, the propensity score-adjusted HR is presented.
CPRD, Clinical Practice Research Datalink; HIRD, HealthCore Integrated Research Database; OAD, oral antidiabetic drug; THIN, The Health Improvement Network.

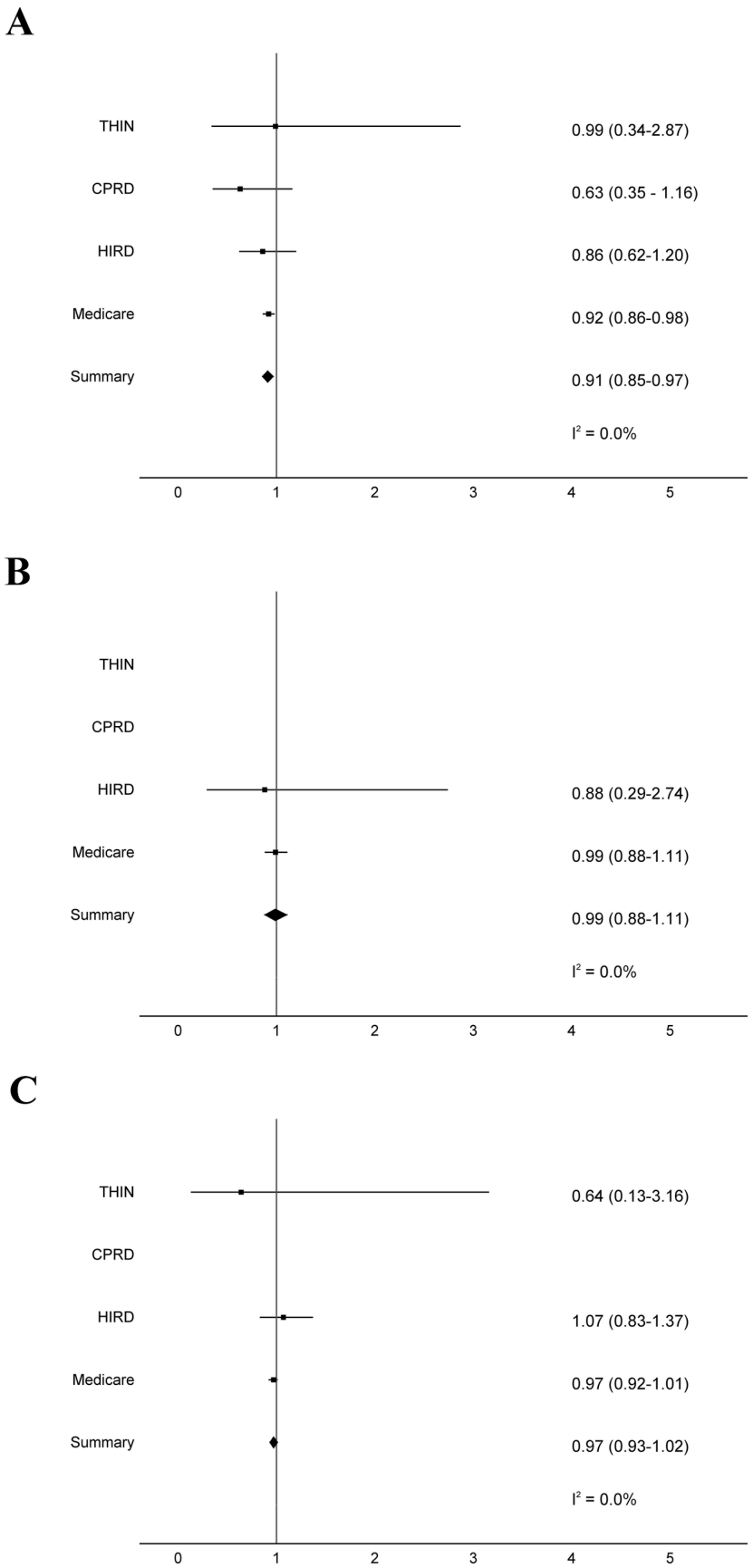

Figure 1 Meta-analyses of HRs (with 95% CIs) of hospitalization with and/or death due to a major adverse cardiovascular event (A), hospitalization for acute kidney injury (B), and hospitalization for infection (C) across the data sources. CPRD, Clinical Practice Research Datalink; HIRD, HealthCore Integrated Research Database; THIN, The Health Improvement Network.

among patients with type 2 diabetes mellitus who initiated saxagliptin compared with those receiving placebo (incidence 1.5% vs 0.4%).[30] A separate analysis of 20 clinical trials comparing hypersensitivity reactions between users of saxagliptin and comparator drugs or placebo found that rates of these events were more common among saxagliptin initiators (incidence rate ratio 1.67, 95% CI, 1.01 to 2.87); however, incidence rates for both groups were low (saxagliptin, 1.3 per 100 person-years; control, 0.8 per 100 person-years).[25] Differences in the definitions of hypersensitivity events between those studies and ours likely accounts for these disparate findings.

Our study has several potential limitations. There is the possibility for unmeasured confounding since not all clinically important variables are consistently captured across these data sources. However, we performed sensitivity analyses to determine the effect of unmeasured variables on measures of effect within each data source and observed that the results were insensitive to unmeasured confounding. Misclassification of both the exposure and outcome is possible. Misclassification of new initiators of saxagliptin or comparator OADs could exist if providers supplied samples or drug rebate cards for varying durations to patients, with no record in the data sources. Moreover, misclassification of new initiators may occur in the UK data sources if the patient was initially prescribed the OAD by a specialist as the general practitioner may not have a record of this initial prescription. Finally, some analyses were based on coding algorithms with <80% PPV or with very few events, limiting our assessment of risk for these end points. However, very few events in a population exceeding 1.0 million indicate that any risk must be very small.

Our analyses have a number of strengths. Using four data sources, rather than a single database, provided a larger sample for safety analyses and allowed inclusion of patients across a variety of settings, within both the USA and UK, and from private and public health insurance plans, enhancing generalizability. We controlled for numerous potential confounding variables using propensity scores. We used standardized definitions for end points and evaluated the validity of diagnostic coding algorithms for these events using medical records. Finally, the 95% CIs surrounding the relative hazards were generally very narrow, indicating a high level of power. Although we cannot completely rule out associations with the outcomes, we can eliminate the likelihood of moderate-to-large associations.

In conclusion, saxagliptin initiation was not associated with increased rates of hospitalized MACE, ALF, AKI, infections, or severe hypersensitivity reactions. The low risk of these events among saxagliptin initiators, particularly in such large study populations, provides real-world evidence of the safety of this medication.

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Contributors VLR and BLS developed the study concept and design. DMC, KH, SEK, PPR, DJM, AJA, KRR, HB, AMG and DBE participated in the acquisition of data. CWN, QL, QW and JAR performed statistical analyses. VLR, DMC, MES, CWN, SEK, PPR and BLS conducted interpretation of the data. VLR and DMC drafted the manuscript. All authors provided critical revisions of the manuscript. VLR is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Ethics approval This study was approved by the UK Independent Scientific Advisory Committees for CPRD (Protocol 10_149RMn) and THIN (Protocol 11-039V), Quorum Review Institutional Review Board for HIRD, and Institutional Review Boards of the University of Pennsylvania and Rutgers University. A data use agreement was obtained from the Centers for Medicare and Medicaid Services.

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REFERENCES

1. Salvatore T, Carbonara O, Cozzolino D, *et al*. Progress in the oral treatment of type 2 diabetes: update on DPP-IV inhibitors. *Curr Diabetes Rev* 2009;5:92–101.
2. Tahrani AA, Piya MK, Barnett AH. Saxagliptin: a new DPP-4 inhibitor for the treatment of type 2 diabetes mellitus. *Adv Ther* 2009;26:249–62.
3. Martin K, Bégaud B, Latry P, *et al*. Differences between clinical trials and postmarketing use. *Br J Clin Pharmacol* 2004;57:86–92.
4. Hall GC, Sauer B, Bourke A, *et al*. Guidelines for good database selection and use in pharmacoepidemiology research. *Pharmacoepidemiol Drug Saf* 2012;21:1–10.
5. Lo Re V, Haynes K, Ming EE, *et al*. Safety of saxagliptin: rationale for and design of a series of postmarketing observational studies. *Pharmacoepidemiol Drug Saf* 2012;21:1202–15.
6. Herrett E, Gallagher AM, Bhaskaran K, *et al*. Data resource profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol* 2015;44:827–36.

7. Horsfall LJ, Nazareth I, Petersen I. Serum uric acid and the risk of respiratory disease: a population-based cohort study. *Thorax* 2014;69:1021–6.
8. Fett N, Haynes K, Propert KJ, *et al*. Five-year malignancy incidence in patients with chronic pruritus: a population-based cohort study aimed at limiting unnecessary screening practices. *J Am Acad Dermatol* 2014;70:651–8.
9. Lewis JD, Schinnar R, Bilker WB, *et al*. Validation studies of the health improvement network (THIN) database for pharmacoepidemiology research. *Pharmacoepidemiol Drug Saf* 2007;16:393–401.
10. Lo Re V, Haynes K, Forde KA, *et al*. Validity of the Health Improvement Network (THIN) for epidemiologic studies of hepatitis C virus infection. *Pharmacoepidemiol Drug Saf* 2009;18:807–14.
11. Carbonari DM, Saine ME, Newcomb CW, *et al*. Use of demographic and pharmacy data to identify patients included within both the Clinical Practice Research Datalink (CPRD) and the Health Improvement Network (THIN). *Pharmacoepidemiol Drug Saf* 2015;24:999–1003.
12. Kamat SA, Gandhi SK, Davidson M. Comparative effectiveness of rosuvastatin versus other statin therapies in patients at increased risk of failure to achieve low-density lipoprotein goals. *Curr Med Res Opin* 2007;23:1121–30.
13. Sarawate C, Sikirica MV, Willey VJ, *et al*. Monitoring anticoagulation in atrial fibrillation. *J Thromb Thrombolysis* 2006;21:191–8.
14. Bullano MF, McNeeley BJ, Yu YF, *et al*. Comparison of costs associated with the use of etanercept, infliximab, and adalimumab for the treatment of rheumatoid arthritis. *Manag Care Interface* 2006;19:47–53.
15. Blumenthal D, Davis K, Guterman S. Medicare at 50--moving forward. *N Engl J Med* 2015;372:671–7.
16. Braitman LE, Rosenbaum PR. Rare outcomes, common treatments: analytic strategies using propensity scores. *Ann Intern Med* 2002;137:693–5.
17. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–58.
18. Lin DY, Psaty BM, Kronmal RA. Assessing the sensitivity of regression results to unmeasured confounders in observational studies. *Biometrics* 1998;54:948–63.
19. Monami M, Dicembrini I, Martelli D, *et al*. Safety of dipeptidyl peptidase-4 inhibitors: a meta-analysis of randomized clinical trials. *Curr Med Res Opin* 2011;27 Suppl 3(Suppl 3):57–64.
20. White WB, Pratley R, Fleck P, *et al*. Cardiovascular safety of the dipetidyl peptidase-4 inhibitor alogliptin in type 2 diabetes mellitus. *Diabetes Obes Metab* 2013;15:668–73.
21. White WB, Cannon CP, Heller SR, *et al*. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med* 2013;369:1327–35.
22. Udell JA, Bhatt DL, Braunwald E, *et al*. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes and moderate or severe renal impairment: observations from the SAVOR-TIMI 53 trial. *Diabetes Care* 2015;38:696–705.
23. Scirica BM, Bhatt DL, Braunwald E, *et al*. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* 2013;369:1317–26.
24. Frederich R, Alexander JH, Fiedorek FT, *et al*. A systematic assessment of cardiovascular outcomes in the saxagliptin drug development program for type 2 diabetes. *Postgrad Med* 2010;122:16–27.
25. Hirshberg B, Parker A, Edelberg H, *et al*. Safety of saxagliptin: events of special interest in 9156 patients with type 2 diabetes mellitus. *Diabetes Metab Res Rev* 2014;30:556–69.
26. Ott C, Raff U, Schmidt S, *et al*. Effects of saxagliptin on early microvascular changes in patients with type 2 diabetes. *Cardiovasc Diabetol* 2014;13:19.
27. Cooper ME, Perkovic V, McGill JB, *et al*. Kidney disease end points in a pooled analysis of individual patient-level data from a large clinical trials program of the dipeptidyl peptidase 4 Inhibitor linagliptin in type 2 diabetes. *Am J Kidney Dis* 2015;66:441–9.
28. Cai L, Cai Y, Lu ZJ, *et al*. The efficacy and safety of vildagliptin in patients with type 2 diabetes: a meta-analysis of randomized clinical trials. *J Clin Pharm Ther* 2012;37:386–98.
29. Amori RE, Lau J, Pittas AG. Efficacy and safety of incretin therapy in type 2 diabetes: systematic review and meta-analysis. *JAMA* 2007;298:194–206.
30. AstraZeneca. AstraZeneca. onglyza (saxagliptin) tablets: US prescribing information (online). 2016 http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022350s014lbl.pdf (accessed 19 Aug 2016).