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=110740) and random samples of up to 10 matched initiators of non-DPP-4 inhibitor OADs within each data source were selected (n=913384). 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/death from 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 reactions 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.

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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). 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 practices6 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 demographic, 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 members12–14 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 demographic, 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 members12–14 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 demographic, 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 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 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, 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/m²). 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. 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 I² statistic.

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. 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
| Characteristic* | Clinical Practice Research Datalink | The Health Improvement Network |
|----------------|-----------------------------------|---------------------------------|
|                | Saxagliptin (n=4181)              | Saxagliptin (n=873)             |
|                | Other OAD (n=40 480)              | Other OAD (n=5564)              |
| Mean (SD) age, years† | 54.65 (11.17) | 53.77 (11.88) | 65.28 (13.11) | 64.87 (13.10) |
| Male sex†       | 2386 (57.1%) | 22 852 (56.5%) | 517 (59.2%) | 3234 (58.1%) |
| UK country†     |                                   |                                 |
| England         | 2775 (66.4%) | 27 347 (67.6%) | 496 (56.8%) | 3507 (63.0%) |
| Northern Ireland| 190 (4.5%)  | 1843 (4.6%)   | 46 (5.3%)  | 246 (4.4%)  |
| Scotland        | 429 (10.3%) | 4235 (10.5%)  | 165 (18.9%) | 1184 (21.3%) |
| Wales           | 787 (18.8%) | 7055 (17.4%)  | 166 (19.0%) | 627 (11.3%)  |
| 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%) |
| Gilbenclamide (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
Table 1  Continued

| Characteristic* | Clinical Practice Research Datalink | The Health Improvement Network |
|-----------------|------------------------------------|--------------------------------|
|                 | Saxagliptin (n=4181) | Other OAD (n=40480) | 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%) | 16166 (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/m²) | 17 (0.4%) | 246 (0.6%) | 0.0283 | 1 (0.1%) | 27 (0.5%) | 0.0678 |
| Normal (18.5–24.9 kg/m²) | 343 (8.2%) | 4449 (11.0%) | 0.0947 | 75 (8.6%) | 633 (11.4%) | 0.0930 |
| Overweight (25.0–29.9 kg/m²) | 1171 (28.0%) | 11811 (29.2%) | 0.0259 | 250 (28.6%) | 1761 (31.6%) | 0.0657 |
| Obese (30–60 kg/m²) | 2621 (62.7%) | 22613 (55.9%) | 0.1393 | 541 (62.0%) | 3039 (54.6%) | 0.1495 |
| Smoking          | 2673 (63.9%) | 24390 (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%) | 59 (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%) | 0.0008 |
| 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%) | 0 (0%) | 0.0000 |
| 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 | 733 (17.5%) | 6149 (15.2%) | 0.0633 | 108 (12.4%) | 743 (13.4%) | 0.0294 |
| Eczema           | 268 (6.4%) | 2092 (5.2%) | 0.0532 | 40 (4.6%) | 283 (5.1%) | 0.0235 |
| Gastrointestinal disease | | | | | | |

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%) | 19 916 (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%) | 11 320 (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%) | 13 997 (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%) | 22 358 (55.2%) | 0.5597 | 718 (82.2%) | 3509 (63.1%) | 0.4406 |
| Antihypertensive agents |                    |                         |                     |                    |                         |                     |
| ACE inhibitors  | 1921 (45.9%) | 13 740 (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
| Characteristic* | Saxagliptin (n=4181) | Other OAD (n=40,880) | Standardized difference§ |
|----------------|---------------------|----------------------|--------------------------|
| Non-aspirin non-steroidal anti-inflammatory | 36 (0.9%) | 342 (0.8%) | 0.0018 |
| Other anticoagulant agents | 1590 (38.0%) | 10,625 (26.2%) | 0.2543 |
| Antiplatelet/anticoagulant agents | 229 (5.5%) | 1,421 (3.5%) | 0.0850 |
| Low-molecular-weight heparin | 10 (0.2%) | 148 (0.4%) | 0.0230 |
| Warfarin | 241 (5.8%) | 1,972 (4.9%) | 0.0390 |
| Other medications | 184 (4.4%) | 1,396 (3.4%) | 0.0286 |
| Immune modulators/immunosuppressants | 56 (1.3%) | 488 (1.2%) | 0.0119 |
| Orexigenic agents | 251 (5.8%) | 1,790 (4.4%) | 0.0714 |
| Urinary antispasmodics | 217 (5.2%) | 1,357 (3.4%) | 0.0910 |
| Psychotropic agents | 912 (21.9%) | 8,094 (20.0%) | 0.0347 |
| Prior OAD therapy‡ | 39 (0.9%) | 29 (0.7%) | 0.0342 |
| Alpha-glucosidase inhibitors: acarbose | 13 (0.3%) | 47 (0.1%) | 0.0425 |
| Biguanide: metformin | 234 (5.6%) | 1,967 (5.0%) | 0.0717 |
| Meglitinides | 46 (1.1%) | 7 (0.2%) | 0.0398 |
| Prior OAD therapy‡ | 40 (1.0%) | 81 (0.2%) | 0.0998 |
| Glucagon-like peptide 1 receptor agonists | 1 (0.0%) | 2 (0.0%) | 0.0187 |
| Sulfonylureas | 1,894 (47.5%) | 1,775 (4.4%) | 0.0717 |
| Other medications | 154 (4.0%) | 7 (0.2%) | 0.0398 |
| Glimepiride | 1,894 (47.5%) | 1,775 (4.4%) | 0.0717 |
| Other medications | 317 (7.9%) | 1,775 (4.4%) | 0.0717 |

Table 1 Continued
| Characteristic* | Saxagliptin (n=873) | Other OAD (n=5564) | Standardized difference§ |
|----------------|---------------------|--------------------|--------------------------|
| Glimepiride    | 212 (5.1%)          | 464 (1.2%)         | 0.2260                   |
| Glipizide      | 52 (1.2%)           | 214 (0.5%)         | 0.0760                   |
| Tolbutamide    | 27 (0.6%)           | 51 (0.1%)          | 0.0839                   |
| Thiazolidinediones | 614 (14.7%)   | 1527 (3.8%)        | 0.3839                   |
| Pioglitazone   | 563 (13.5%)         | 1107 (2.9%)        | 0.3933                   |
| Rosiglitazone  | 54 (1.3%)           | 427 (1.1%)         | 0.0219                   |

*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.
§Standardized difference was calculated as the difference in mean (or proportion for binary variables) divided by the SD (pooled SD for continuous variables).

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).

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.

There was no association between saxagliptin initiation and hospitalization for AKI across the data sources (table 3). Meta-analysis of results within THIN, Medicare, and HIRD showed 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.

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.

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.
| Characteristic*                                      | Medicare (n=92,577) | Other OAD (n=740,328) | Standardized difference§ | Saxagliptin (n=10,521) | Other OAD (n=100,343) | 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                   | 2,245 (21.3%)          | 21,668 (21.6%)         | 0.0062                   |
| East South Central                                  | 8921 (9.6%)         | 71,154 (9.6%)         | 0.0009                   | 10,88 (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                   | 1,463 (13.9%)          | 14,209 (14.2%)         | 0.0073                   |
| South Atlantic                                       | 22,116 (23.9%)      | 177,647 (24.0%)       | 0.0025                   | 3,135 (29.8%)          | 29,474 (29.4%)         | 0.0093                   |
| West North Central                                   | 4896 (5.3%)         | 37,258 (5.0%)         | 0.0116                   | 548 (5.2%)             | 5,339 (5.3%)           | 0.0050                   |
| West South Central                                   | 11,900 (12.9%)      | 97,790 (13.2%)        | 0.0105                   | 240 (2.3%)             | 2,025 (2.0%)           | 0.0181                   |
| Other OAD initiated at index date                   |                     |                       |                          |                        |                        |                          |
| Alpha-glucosidase inhibitors                        | 0 (0%)              | 4,334 (0.6%)          | –                        | 0 (0%)                 | 3,43 (0.3%)            | –                        |
| Acarbose                                            | 0 (0%)              | 4,050 (0.5%)          | –                        | 0 (0%)                 | 313 (0.3%)             | –                        |
| Miglitol                                            | 0 (0%)              | 284 (0.0%)            | –                        | 0 (0%)                 | 30 (0.0%)              | –                        |
| Biguanide: metformin                                | 0 (0%)              | 3,883,85 (52.5%)      | –                        | 0 (0%)                 | 7,094 (70.7%)          | –                        |
| Meglitinides                                         | 0 (0%)              | 17,007 (2.3%)         | –                        | 0 (0%)                 | 802 (0.8%)             | –                        |
| Nateglinide                                         | 0 (0%)              | 7,652 (1.0%)          | –                        | 0 (0%)                 | 374 (0.4%)             | –                        |
| Repaglinide                                         | 0 (0%)              | 9,355 (1.3%)          | –                        | 0 (0%)                 | 428 (0.4%)             | –                        |
| Sodium-glucose cotransporter 2: canagliflozin       | 0 (0%)              | –                     | –                        | 0 (0%)                 | 313 (0.3%)             | –                        |
| Sulfonylureas                                       | 0 (0%)              | 2,588,86 (35.0%)      | –                        | 0 (0%)                 | 21,196 (21.1%)         | –                        |
| Chlorpropamide                                      | 0 (0%)              | 141 (0.0%)            | –                        | 0 (0%)                 | 6 (0.0%)               | –                        |
| Glimpiride                                          | 0 (0%)              | 85,584 (11.6%)        | –                        | 0 (0%)                 | 7,860 (7.8%)           | –                        |
| Glibizide                                           | 0 (0%)              | 110,556 (14.9%)       | –                        | 0 (0%)                 | 8,098 (8.1%)           | –                        |
| Glyburide (glibenclamide in UK data sources)        | 0 (0%)              | 61,794 (8.3%)         | –                        | 0 (0%)                 | 5,182 (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%)                 | 6,620 (6.6%)           | –                        |
| Pioglitazone                                         | 0 (0%)              | 67,603 (9.1%)         | –                        | 0 (0%)                 | 6,295 (6.3%)           | –                        |
| Rosiglitazone                                       | 0 (0%)              | 3,651 (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                   | 1,073 (10.2%)          | 8,469 (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)| 9607 (10.4%)        | 77,376 (10.5%)        | 0.0024                   | 242 (2.3%)             | 2,288 (2.3%)           | 0.0013                   |

Continued
Table 2 Continued

| Characteristic* | Medicare | Other OAD | Standardized difference§ | Medicare | Other OAD | Standardized difference§ |
|-----------------|----------|-----------|---------------------------|----------|-----------|---------------------------|
|                 | Saxagliptin (n=92577) | Other OAD (n=740328) | | Saxagliptin (n=10521) | Other OAD (n=100343) | |
| Coronary artery disease, congestive heart failure, ventricular tachycardia/ fibrillation | 36836 (39.8%) | 279939 (37.8%) | 0.0406 | 1203 (11.4%) | 10791 (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 | 18387 (19.9%) | 118385 (16.0%) | 0.1010 | 544 (5.2%) | 3549 (3.5%) | 0.0801 |
| Neuropathy | 20973 (22.7%) | 138634 (18.7%) | 0.0971 | 884 (8.4%) | 6599 (6.6%) | 0.0694 |
| Peripheral vascular disease | 16822 (18.2%) | 122379 (16.5%) | 0.0433 | 410 (3.9%) | 3266 (3.3%) | 0.0346 |
| Retinopathy | 12102 (13.1%) | 77603 (10.5%) | 0.0804 | 539 (5.1%) | 3665 (3.7%) | 0.0718 |
| Unspecified additional diabetic complications | 7123 (7.7%) | 51544 (7.0%) | 0.0281 | 407 (3.9%) | 2714 (2.7%) | 0.0653 |
| Medical comorbidities | | | | | | |
| Allergic rhinitis/hay fever | 6430 (6.9%) | 41153 (5.6%) | 0.0573 | 542 (5.2%) | 4623 (4.6%) | 0.0253 |
| Asthma | 7001 (7.6%) | 57683 (7.8%) | 0.0086 | 407 (3.9%) | 4300 (4.3%) | 0.0211 |
| Chronic obstructive pulmonary disease/ bronchitis | 11171 (12.1%) | 97901 (13.2%) | 0.0348 | 286 (2.7%) | 2949 (2.9%) | 0.0133 |
| Dermatological disorders | | | | | | |
| Eczema | 3240 (3.5%) | 22611 (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%) | 16763 (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 | 71221 (76.9%) | 492578 (66.5%) | 0.2324 | 6550 (62.3%) | 48349 (48.2%) | 0.2859 |
| Hypertension | 78403 (84.7%) | 577668 (78.0%) | 0.1717 | 6397 (60.8%) | 50751 (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%) | 10146 (1.4%) | 0.0106 | 63 (0.6%) | 574 (0.6%) | 0.0035 |
| Solid organ | 7837 (8.5%) | 63813 (8.8%) | 0.0055 | 339 (3.2%) | 3174 (3.2%) | 0.0034 |
| Obesity | 10711 (11.6%) | 84346 (11.4%) | 0.0055 | 1006 (9.6%) | 9899 (9.9%) | 0.0102 |
| Rheumatoid arthritis | 2538 (2.7%) | 18429 (2.5%) | 0.0158 | 90 (0.9%) | 843 (0.8%) | 0.0017 |
| Medications | | | | | | |
| Acetaminophen/ paracetamol | 24456 (26.4%) | 194424 (26.3%) | 0.0035 | 2091 (19.9%) | 19897 (19.8%) | 0.0011 |
| Antiallergic agents | 12734 (13.8%) | 92459 (12.5%) | 0.0375 | 836 (7.9%) | 7720 (7.7%) | 0.0094 |
| Antibacterials | 35628 (38.5%) | 257225 (34.7%) | 0.0777 | 3286 (31.2%) | 29277 (29.2%) | 0.0448 |
| Anticonvulsants | 4707 (5.1%) | 41871 (5.7%) | 0.0253 | 768 (7.3%) | 7682 (7.7%) | 0.0135 |
| Antifungals | 9132 (9.9%) | 60580 (8.2%) | 0.0587 | 735 (7.0%) | 5858 (5.8%) | 0.0469 |
| Antihistamines | 9142 (9.9%) | 61223 (8.3%) | 0.0559 | 645 (6.1%) | 5406 (5.4%) | 0.0319 |

Continued
Table 2  Continued

| Characteristic* | Medicare (n=92577) | Other OAD (n=740328) | Standardized difference§ | Medicare (n=10521) | Other OAD (n=100343) | Standardized difference§ |
|----------------|--------------------|----------------------|--------------------------|--------------------|----------------------|--------------------------|
| Antihyperlipidemic agents | Saxagliptin 59126 (63.9%) Other OAD 375758 (50.8%) | 0.2674 | Saxagliptin 5233 (49.7%) Other OAD 35934 (35.8%) | 0.2843 |
| Antihypertensive agents | ACE inhibitors 38296 (41.4%) Other OAD 278503 (37.6%) | 0.0767 | ACE inhibitors 3736 (35.5%) Other OAD 27518 (27.4%) | 0.1748 |
| | Angiotensin receptor blockers 25262 (27.3%) Other OAD 133659 (18.1%) | 0.2219 | Angiotensin receptor blockers 2034 (19.3%) Other OAD 13433 (13.4%) | 0.1613 |
| | Beta blockers 38938 (42.1%) Other OAD 268421 (36.3%) | 0.1191 | Beta blockers 2219 (21.1%) Other OAD 18338 (18.3%) | 0.0709 |
| | Calcium channel blockers 28176 (30.4%) Other OAD 194430 (26.3%) | 0.0927 | Calcium channel blockers 1670 (15.9%) Other OAD 13557 (13.5%) | 0.0668 |
| | Loop diuretics 19448 (21.0%) Other OAD 131150 (17.7%) | 0.0834 | Loop diuretics 524 (5.0%) Other OAD 4726 (4.7%) | 0.0126 |
| Other antihypertensive agents | 10023 (10.8%) Other OAD 65686 (8.9%) | 0.0656 | 474 (4.5%) Other OAD 3840 (3.8%) | 0.0340 |
| Thiazide diuretics | 18813 (20.3%) Other OAD 113540 (15.3%) | 0.1305 | 1846 (17.5%) Other OAD 14470 (14.4%) | 0.0854 |
| Antivirals | 2005 (2.2%) Other OAD 15077 (2.0%) | 0.0090 | 197 (1.9%) Other OAD 2468 (2.5%) | 0.0403 |
| | Non-aspirin non-steroidal anti-inflammatory agents 15506 (16.7%) Other OAD 109437 (14.8%) | 0.0540 | Non-aspirin non-steroidal anti-inflammatory agents 1488 (14.1%) Other OAD 13098 (13.1%) | 0.0318 |
| Other antiplatelet/ anticoagulant agents | Aspirin 644 (0.7%) Other OAD 4504 (0.6%) | 0.0108 | Aspirin 16 (0.2%) Other OAD 142 (0.1%) | 0.0028 |
| | Clopidogrel 11150 (12.0%) Other OAD 69439 (9.4%) | 0.0862 | Clopidogrel 363 (3.5%) Other OAD 3035 (3.0%) | 0.0240 |
| | Low-molecular-weight heparin 372 (0.4%) Other OAD 3889 (0.5%) | 0.0182 | Low-molecular-weight heparin 32 (0.3%) Other OAD 288 (0.3%) | 0.0032 |
| | Warfarin 6459 (7.0%) Other OAD 51316 (6.9%) | 0.0018 | Warfarin 203 (1.9%) Other OAD 1652 (1.6%) | 0.0214 |
| Other medications | Allopurinol 4924 (5.3%) Other OAD 31821 (4.3%) | 0.0477 | Allopurinol 270 (2.6%) Other OAD 2408 (2.4%) | 0.0107 |
| | Antiarrhythmics 11895 (12.8%) Other OAD 88324 (11.9%) | 0.0279 | Antiarrhythmics 489 (4.6%) Other OAD 4407 (4.4%) | 0.0123 |
| | Immune modulators/ immunosuppressants 3986 (4.3%) Other OAD 29604 (4.0%) | 0.0154 | Immune modulators/ immunosuppressants 223 (2.1%) Other OAD 2400 (2.4%) | 0.0183 |
| | Nitroglycerin 3995 (4.3%) Other OAD 27908 (3.8%) | 0.0277 | Nitroglycerin 137 (1.3%) Other OAD 1241 (1.2%) | 0.0058 |
| | Urinary antispasmodics 4692 (5.1%) Other OAD 32809 (4.4%) | 0.0299 | Urinary antispasmodics 112 (1.1%) Other OAD 1185 (1.2%) | 0.0110 |
| Psychotropic agents | Antidepressants 24264 (26.2%) Other OAD 186970 (25.3%) | 0.0218 | Antidepressants 1992 (18.9%) Other OAD 18828 (18.8%) | 0.0043 |
| | Antipsychotics 6305 (6.8%) Other OAD 54109 (7.3%) | 0.0195 | Antipsychotics 222 (2.1%) Other OAD 2197 (2.2%) | 0.0055 |
| | Prior OAD therapy‡ 68160 (73.6%) Other OAD 273289 (36.9%) | 0.7944 | Prior OAD therapy‡ 6957 (66.1%) Other OAD 21797 (21.7%) | 1.0004 |
| | Alpha-glucosidase inhibitors 715 (0.8%) Other OAD 1988 (0.3%) | 0.0701 | Alpha-glucosidase inhibitors 38 (0.4%) Other OAD 118 (0.1%) | 0.0499 |
| | Acarbose 636 (0.7%) Other OAD 1730 (0.2%) | 0.0668 | Acarbose 35 (0.3%) Other OAD 108 (0.1%) | 0.0479 |
| | Miglitol 84 (0.1%) Other OAD 260 (0.0%) | 0.0222 | Miglitol 4 (0.0%) Other OAD 10 (0.0%) | 0.0181 |
| | Biguanide: metformin 46101 (49.8%) Other OAD 140212 (39.8%) | 0.2013 | Biguanide: metformin 5500 (52.3%) Other OAD 12578 (42.8%) | 0.1909 |
| | Meglitinides 2430 (2.6%) Other OAD 7708 (1.0%) | 0.1183 | Meglitinides 140 (1.3%) Other OAD 375 (0.4%) | 0.1042 |
| | Nateglinide 1235 (1.3%) Other OAD 3467 (0.5%) | 0.0911 | Nateglinide 75 (0.7%) Other OAD 182 (0.2%) | 0.0796 |
| | Repaglinide 1231 (1.3%) Other OAD 4286 (0.6%) | 0.0764 | Repaglinide 67 (0.6%) Other OAD 193 (0.2%) | 0.0691 |
| | Sodium-glucose cotransporter 2: canagliflozin – – – Other OAD 5 (0.0%) | 10 (0.0%) | Sodium-glucose cotransporter 2: canagliflozin – – – Other OAD 5 (0.0%) | 10 (0.0%) | 0.0221 |
| | Sulfonylureas 36848 (39.8%) Other OAD 127737 (17.3%) | 0.5157 | Sulfonylureas 2874 (27.3%) Other OAD 8168 (8.1%) | 0.5187 |
| | Chlorpropamide 21 (0.0%) Other OAD 221 (0.0%) | 0.0044 | Chlorpropamide 1 (0.0%) Other OAD 3 (0.0%) | 0.0082 |

Continued
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.25 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 26 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

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**Table 2 Continued**

| Characteristic* | Medicare       | Other OAD      | Standardized difference§ | HealthCore Integrated Researc Database |
|----------------|----------------|----------------|--------------------------|---------------------------------------|
| Glimepiride    | 14315 (15.5%)  | 35805 (5.5%)  | 0.3309                   | 1262 (12.0%) 2759 (3.0%) 0.3475       |
| Glipizide      | 15451 (16.7%)  | 56241 (8.9%)  | 0.2338                   | 1139 (10.8%) 3591 (3.9%) 0.2679       |
| Glyburide      | 8116 (8.8%)    | 36892 (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 | 18258 (19.7%) | 54840 (7.4%)  | 0.3656                   | 1376 (13.1%) 4832 (4.8%) 0.2926       |
| Pioglitazone   | 16698 (18.0%)  | 45435 (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.
### 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 | 70271 | 39300.8 | 1030 | 26.2 (24.6 to 27.9) | 562159 | 308101.7 | 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)  | 89538 | 41694.0 | 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)  | 35916 | 20245.3 | 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† | 72831 | 41011.4 | 28   | 0.7 (0.5 to 1.0)  | 72831 | 37260.1 | 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) | 90174 | 42230.7 | 6    | 0.1 (0.05 to 0.3) | 2.97 (0.49 to 18.1)‡ |
| CPRD†     | 3794  | 2581.4 | 0    | 0.0 (0.0 to 1.2)  | 36196 | 20549.8 | 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 | 61888 | 34597.7 | 334  | 9.7 (8.6 to 10.7) | 519259 | 289326.5 | 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)  | 87770 | 40979.4 | 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)  | 32798 | 18369.1 | 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 | 74263 | 41012.6 | 2280 | 55.6 (53.3 to 57.9) | 577572 | 314496.9 | 17840 | 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) | 89485 | 41773.4 | 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) | 35417 | 19687.2 | 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‡ | 77857 | 43764.4 | 75   | 1.7 (1.3 to 2.1)  | 624074 | 342886.0 | 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)  | 91814 | 42887.8 | 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) | 36245 | 20558.8 | 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%). 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). 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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Ethics approval This study was approved by the UK Independent Scientific Advisory Committee for CPRD (Protocol 10_149Rm) and THIN (Protocol 11-039R), 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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