1. ABSTRACT

Name of company: Boehringer Ingelheim International GmbH			
Name of finished medicinal product: Jardiance Synjardy			
Name of active ingredient: A10BK03 Empagliflozin A10BD20 Empagliflozin/metformin			
Report date: 11 Nov 2022	**Study number:** 1245.96	**Version/Revision:** 1.0	**Version/Revision date:** NA
Title of study:	Post-authorisation safety study in patients with type 2 diabetes mellitus to assess the risk of acute liver injury, acute kidney injury and chronic kidney disease, severe complications of urinary tract infection, genital infections, and diabetic ketoacidosis among patients treated with empagliflozin compared with patients treated with DPP-4 inhibitors		
Keywords:	Empagliflozin, DPP-4 inhibitor, liver injury, kidney injury, severe complications of urinary tract infection, genital infection, diabetic ketoacidosis		
Rationale and background:	Jardiance (empagliflozin), a highly potent and selective inhibitor of sodium-glucose cotransporter 2 (SGLT2), was approved in Europe in May 2014 for the treatment of type 2 diabetes mellitus (T2D) to improve glycaemic control in adults. SGLT2 is highly expressed in the kidney; as the predominant glucose transporter, it is responsible for the reabsorption of glucose from the glomerular filtrate back into the circulation. Empagliflozin improves glycaemic control in patients with T2D by reducing renal glucose reabsorption [R14-4617]. As part of the risk management plan, Boehringer Ingelheim International GmbH (BI) committed to conduct a post-authorisation safety study (PASS) to evaluate the liver safety [acute liver injury (ALI)] of empagliflozin due to a higher frequency of serious hepatic events in clinical trials and renal safety [acute kidney injury (AKI) and chronic kidney disease (CKD)] of empagliflozin due to its mechanism of action. The study also evaluated the risks of severe complications of urinary tract infection (UTI) and genital infections (GI). The rationale for looking at these risks is related to the mechanism of action of empagliflozin; the inhibition of SGLT2 in patients with T2D leads to excess glucose excretion in the urine [R14-4617], which, together with hyperglycaemia and T2D-related comorbidities and complications, may be an important cause of increased susceptibility of patients with diabetes to UTI and GI. In addition,		

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	as a safety topic of interest, the study also assessed the risks of diabetic ketoacidosis (DKA) due to DKA events occurring in patients taking SGLT2 inhibitors for T2D; a number of these events have been atypical, i.e., blood sugar levels not as high as expected or even in the normal range [P15-08785].
Research question and objectives:	To estimate, among patients with T2D, the risk of ALI, the risk of AKI, the risk of CKD, the risk of severe complications of UTI, the risk of GI, and the risk of DKA among patients treated with empagliflozin compared with patients treated with DPP-4 inhibitors.
Study design:	This was a non-interventional observational cohort study using existing data from routine medical care in the Clinical Practice Research Datalink (CPRD) in the United Kingdom (UK), the Danish Population Registries (Danish Registries) in Denmark, and the HealthCore Integrated Research Database (HIRD®) in the United States (US). The study used a new-user design and compared initiators of empagliflozin with initiators of DPP-4 inhibitors. Propensity scores, based on information before or at the index date, were used to account for potential confounding. The index date was defined as the date on which each identified initiator received the index prescription for empagliflozin or a DPP-4 inhibitor.
Setting:	The study was performed in CPRD in the UK (both the General Practitioner Online Database [GOLD] and Aurum). For evaluation of the rarest outcomes (i.e., ALI, AKI, and DKA) the study was also performed in the Danish Registries in Denmark and in HIRD in the US. The study period started on 01 August 2014, the date of empagliflozin launch in the UK, US, and Denmark. The study period end date was 01 August 2019 (31 July 2019 in HIRD). All data sources completed data extraction for the full study period.
Subjects and study size, including dropouts:	The study population included all eligible patients with T2D initiating treatment with empagliflozin or with a DPP-4 inhibitor during the study period. Eligible patients were included if they were aged 18 or more years

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and had at least 12 months of continuous registration before or at the index date in the data source.

- Each member of the empagliflozin-exposed population had to have at least 1 prescription/dispensing for empagliflozin, with or without other glucose-lowering drugs (GLDs), and no prior prescription/dispensing of empagliflozin, other SGLT2 inhibitors, or DPP-4 inhibitors during the 12 months before or on the index date.
- Each member of the population exposed to a DPP-4 inhibitor had to have at least 1 prescription/dispensing for a DPP-4 inhibitor, with or without other GLDs, and no prior prescription/dispensing of a DPP-4 inhibitor, empagliflozin, or other SGLT2 inhibitor during the 12 months before or on the index date.

Initiators of the study drugs were subclassified based on whether they were (1) switching from monotherapy with another GLD to monotherapy with a study drug, (2) switching from dual or triple therapy with another GLD to dual or triple therapy with a study drug and other GLDs, (3) adding a study drug to therapy with 1 or 2 other GLDs to become patients on dual or triple therapy or (4) naive to GLD treatment and starting the study drug as first-line therapy. Treatment complexity was considered in the analysis. Prior or current use of insulin was allowed, and an additional stratified analysis by insulin use was done.

Only patients with T2D were included in the study. Patients with type 1 diabetes (T1D) were excluded. Algorithms to identify T2D and T1D were adapted to the type and availability of data in each data source. Different exclusion criteria were applied according to each outcome of interest (e.g., patients with CKD were excluded from the analysis of AKI), which resulted in different outcome-specific populations (see Section 9.3.8).

Follow-up started the day after the index date and, for each specified outcome, continued until the occurrence of the study outcome, end of study data, the date during follow-up on which specific exclusion criteria were met, the end date of the first continuous treatment episode of the index drug

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	(empagliflozin or DPP-4 inhibitor) plus a defined grace period (30 days after the end of the last prescription's days' supply in main analyses), or the date on which a new treatment episode started with the other type of study drug or other SGLT2 inhibitors.
Variables and data sources:	*Exposures (index drugs):* • Empagliflozin (including fixed-dose combination with metformin) • DPP-4 inhibitors: sitagliptin, saxagliptin, linagliptin, vildagliptin, alogliptin (and fixed-dose combinations of these drugs with metformin) Fixed-dose combinations of SGLT2 inhibitors with DPP-4 inhibitors were not included in the study. Current use of the index drugs was defined from the date of prescription/dispensing of empagliflozin or a DPP-4 inhibitor to the end of days' supply for that prescription, plus a period of 30 days. Recent use was defined from the end of current use (30 days after end of supply) through 90 days later (i.e., 120 days after end of supply). End of days' supply was estimated according to prescription instructions in CPRD or based on available information on the duration of dispensings (e.g., number of packages bought, strength, and number of pills) in Danish Registries and HIRD. *Outcomes:* • DKA (hospitalisation or emergency department [ED] visit)—primary outcome, in all data sources • ALI in patients without predisposing conditions (hospitalisation, ED visit, or specialist visit)—primary outcome, in all data sources (ALI1) • ALI in patients with and without predisposing conditions (hospitalisation, ED visit, or specialist visit)—secondary outcome, in all data sources (ALI2)

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- AKI (hospitalisation, ED visit, or specialist visit)—primary outcome, in all data sources
- CKD (inpatient and outpatient)—secondary outcome, only in CPRD
- Severe complications of UTI (inpatient and outpatient)—primary outcome, only in CPRD
- GI (inpatient and outpatient)—primary outcome, only in CPRD
- Severe GI (hospitalisation or ED visit or that required systemic treatment)—secondary outcome, only in CPRD

Post-authorisation studies based on secondary use of data, such as the one described in this report, do not require the reporting of adverse reactions in the form of individual case safety reports.

Sensitivity analysis outcomes:

Sensitivity analyses (ALI1S and AKIS) were performed by adding outpatient primary care events of ALI and AKI to the ALI and AKI primary outcomes. These analyses were performed only in CPRD and HIRD, where primary care data were available.

Validation:

Validation of events identified by the algorithms was implemented for all outcomes in the 3 data sources. In the Danish Registries, validation was conducted for 80% to 90% of all events identified using the available electronic laboratory results. In CPRD and HIRD, a random sample of up to 200 events of each outcome were targeted for validation. If the number of events identified for any of the outcomes was 200 or fewer, all events for which further information could be obtained were validated for those outcomes. Otherwise, a random sample of events was selected. Events identified in CPRD and Hospital Episode Statistics (HES) were validated through questionnaires sent to general practitioners (GPs), complemented with available laboratory results. Events identified in HIRD were validated through medical record data abstraction.

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Data sources:

The data sources included in the study were CPRD in the UK, and for the evaluation of the rarest outcomes, i.e., ALI, AKI and DKA, also the Danish Registries in Denmark and HIRD in the US.

CPRD contains diagnostic and prescribing information recorded by GPs as part of their routine clinical practice in the UK. At the end of the study period (01 August 2019), the data source contained data for over 17.5 million patients in CPRD GOLD and 23.8 million patients in CPRD Aurum. At that time, CPRD was representative of the UK population in terms of age and sex, with research-quality data from 840 UK practices in CPRD GOLD and 895 practices in CPRD Aurum; 2.9 million patients in CPRD GOLD and 8.4 million patients in CPRD Aurum were active [R22-2437, R22-2438]. Detailed information on prescriptions written by the GPs, including prescribed dose and duration, is routinely recorded in CPRD. Additional diagnostic and treatment information can be found in letters from specialists, hospitals, and other sources.

The **Danish Registries**. The Danish healthcare system provides universal coverage to all Danish residents (5.9 million inhabitants [R20-2510, R22-2424]). The registries used in the study were the Danish National Patient Register, which includes data on all hospital admissions since 1 January 1977 and on specialist outpatient hospital clinic and ED visits since 1995, and the National Health Services Prescription Database, which encompasses the reimbursement records of all reimbursed drugs sold in community pharmacies and hospital-based outpatient pharmacies in Denmark since 2004. The national health registries can be linked to all other national databases through the unique Civil Personal Registration Number. No primary care diagnosis data are available for research purposes, but the new nationwide Register of Laboratory Results for Research (LAB_F) tracks all laboratory test results from both primary and secondary care.

HIRD contains geographically diverse longitudinal medical and pharmacy claims data from approximately 50 million health plan members across the

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	US [R22-3646]. Member enrolment, medical care (professional and facility claims), outpatient prescription drug use, outpatient laboratory test result data (available for ~30% of the patients), and healthcare utilisation may be tracked for health plan members dating back to January 2006. For approximately 50% of members, data in HIRD can be linked to inpatient and outpatient medical records (source records for validation).
Results:	After applying all common inclusion and exclusion criteria, and before trimming, 76,174 initiators of empagliflozin and 257,406 initiators of DPP-4 inhibitors were included in the DKA populations (which were the largest populations and had no outcome-specific exclusion criteria). The number of patients included in the other outcome-specific populations were smaller, with the exclusion criteria for ALI1 (acute liver injury in patients with no predisposing conditions [primary outcome]) being the most restrictive. Most patients (71%-87%) initiated empagliflozin and DPP-4 inhibitors as add-on therapy, and more than 70% of the initiators of empagliflozin and of DPP-4 inhibitors were also users of metformin. The most relevant difference in treatment patterns observed between the 2 exposure cohorts was concomitant use of insulin, which was consistently more frequent in empagliflozin initiators than in DPP-4 inhibitor initiators in all data sources. Duration of exposure was shorter among initiators of empagliflozin than among initiators of DPP-4 inhibitors. Baseline characteristics before trimming and before propensity score adjustment showed that empagliflozin initiators were younger than initiators of DPP-4 inhibitors. In the populations used to evaluate DKA, among the empagliflozin cohort, the mean (standard deviation [SD]) age was 57.8 (10.9) years in CPRD, 55.4 (9.9) years in HIRD, 60.8 (11.5) years in Danish Registries, and 57.2 (10.8) years in the pooled DKA population. Among the DPP-4 inhibitors cohort, the mean (SD) age was 65.5 (13.2) years in CPRD, 58.1 (12.0) years in HIRD, 65.8 (12.9) years in Danish Registries, and 62.1 (13.1) years in the pooled DKA population. A similar age distribution was observed in other outcome-specific populations. Approximately 60% were

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males (192,152 in the pooled DKA population) and 40% were females (141,428 in the pooled DKA population) in both cohorts and in all data sources. Patients in the empagliflozin cohort were more frequently obese than those in the DPP-4 inhibitors cohort. There was a higher proportion of patients on DPP-4 inhibitors in the initial years and a higher proportion of empagliflozin initiators in the later years of the study in all data sources. The average pretreatment HbA1c (glycated haemoglobin) was higher in empagliflozin than DPP-4 inhibitor initiators, and the proportion of patients with poor diabetes control, i.e., HbA1c > 74.9 mmol/mol or HbA1c > 9.0%, was higher in the empagliflozin cohort than in the DPP-4 inhibitors cohort in CPRD and Danish Registries. The proportions of patients with diabetes complications were similar between cohorts in all data sources, except for "other diabetes complications," which were more frequent in the empagliflozin cohort than in the DPP-4 inhibitors cohort in HIRD and in Danish Registries. The distribution of other baseline comorbidities and medications was similar between exposure cohorts in all data sources.

When evaluating propensity score distributions, non-overlapping propensity score curves were observed in Danish Registries. Non-comparability was solved by stratifying the Danish study population into patients with fewer than 3 GLDs and patients with 3 or more GLDs. After trimming, a good balance in the distribution of all variables was achieved in all data sources.

The number of events identified was the lowest for ALI1 (< 70 in the empagliflozin cohort), followed by DKA, ALI2, and AKI. For other outcomes, more than 1,000 events were identified.

The validation results had several limitations. These related mainly to the low response for GP questionnaires in CPRD and the low retrieval rates of medical records in HIRD, which impacted the precision of the positive predictive value (PPVs) for some outcomes in those 2 data sources.

After trimming, 64,599 initiators of empagliflozin and 203,315 initiators of DPP-4 inhibitors were included in the DKA pooled population. DKA was more frequent among initiators of empagliflozin (adjusted incidence rate [IR]

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per 1,000 person-years, range, 1.50 to 3.62) than among initiators of DPP-4 inhibitors (adjusted IR per 1,000 person-years, range, 0.70 to 1.82), except in those using 3 or more GLDs in Danish Registries, among whom the adjusted IR was < 0.2 per 1,000 person-years. Initiators of empagliflozin had an approximately 2-fold increased risk of DKA compared with initiators of DPP-4 inhibitors (pooled adjusted incidence rate ratio [IRR], 2.19; 95% CI, 1.74-2.76). Results for DKA were consistent in all data sources, with clearly increased IRRs with empagliflozin use, except among the small subset of patients using 3 or more GLDs in Danish Registries, although this was based on a low number of DKA events and led to very imprecise estimates that were compatible with a range of risk from an 80% decreased risk of DKA to a 100% increased risk of DKA.

Prior to trimming, 56,939 initiators of empagliflozin and 194,488 initiators of DPP-4 inhibitors were included in the ALI1 pooled population, and the number after trimming cannot be reported due to small cell count policies.[1] After trimming, 69,917 initiators of empagliflozin and 197,172 initiators of DPP-4 inhibitors were included in the ALI2 pooled population. Acute liver injury events were less common among initiators of empagliflozin (adjusted IR per 1,000 person-years, range, 0.02 to 1.21 for ALI1 and 1.23 to 4.19 for ALI2) than among initiators of DPP-4 inhibitors (adjusted IR per 1,000 person-years, range, 0.09 to 1.41 for ALI1 and 1.86 to 5.47 for ALI2). Based on the point estimates of the adjusted IRR, a decreased risk of liver outcomes was observed among initiators of empagliflozin compared with initiators of DPP 4 inhibitors—ALI1 (pooled adjusted IRR, 0.77; 95% CI, 0.50-1.19) and ALI2 (pooled adjusted IRR, 0.70; 95% CI, 0.56-0.88). However, the precision of the estimates was low, especially for ALI1. Results for ALI1 and ALI2 were generally similar and consistent across all data sources and in both Danish population subsets. When including outpatient events (ALI1S), ALI

[1] The number of patients included after trimming in the ALI1 pooled population cannot be reported since the number of events in Danish Registries was 1 to 4, and the total cannot be given to avoid back-calculation of values due to the Danish small cell count policy.

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became slightly more frequent (adjusted IR per 1,000 person-years, range, 1.22 to 8.59), but its incidence was still lower among initiators of empagliflozin, and the observed decreased risk when compared with initiators of DPP-4 inhibitors persisted. Among patients with relevant laboratory results available, in all data sources and irrespective of ALI diagnosis, elevated liver enzymes during follow-up were reported for less than 2% of patients in each exposure cohort. In all data sources, however, that percentage was higher in the DPP-4 inhibitors cohort than in the empagliflozin cohort.

After trimming, 58,393 initiators of empagliflozin and 167,823 initiators of DPP-4 inhibitors were included in the AKI pooled population. Acute kidney injury events were less common among initiators of empagliflozin (adjusted IR per 1,000 person-years, range, 2.98 to 10.84) than among initiators of DPP-4 inhibitors (adjusted IR per 1,000 person-years, range, 5.30 to 15.98). A decreased risk of AKI was observed among initiators of empagliflozin compared with initiators of DPP-4 inhibitors (pooled adjusted IRR, 0.54; 95% CI, 0.41-0.73). When including outpatient events (AKIS), the adjusted IRs increased slightly (an increase of less than 1 per 1,000 person-years), and the decreased risk when compared with initiators of DPP-4 inhibitors persisted.

After trimming, 13,256 initiators of empagliflozin and 62,435 initiators of DPP-4 inhibitors included in the CKD population in CPRD. Chronic kidney disease was evaluated only in CPRD and was less frequent among initiators of empagliflozin (adjusted IR, 10 per 1,000 person-years) than among initiators of DPP-4 inhibitors (adjusted IR, 19 per 1,000 person-years), leading to a 47% decreased risk (adjusted IRR, 0.53; 95% CI, 0.43-0.65) among initiators of empagliflozin compared with initiators of DPP-4 inhibitors.

After trimming, 14,050 initiators of empagliflozin and 77,330 initiators of DPP-4 inhibitors were included in the UTI population in CPRD. Severe complications of UTI were evaluated only in CPRD and were less frequent

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among initiators of empagliflozin (adjusted IR, 3.32 per 1,000 person-years) than among initiators of DPP-4 inhibitors (adjusted IR, 6.47 per 1,000 person-years), leading to a 49% decreased risk of severe UTI among initiators of empagliflozin compared with initiators of DPP-4 inhibitors (adjusted IRR, 0.51; 95% CI, 0.37-0.72).

Genital infections in males and females (GIM and GIF, respectively) and severe GI in males and females (GIMH and GIFH, respectively) were evaluated only in CPRD. The majority of the severe GI events were classified as severe due to the criterion of receiving systemic treatment with oral antifungals or antibiotics. These were not necessarily clinically severe events in all cases. After trimming, 8,272 initiators of empagliflozin and 45,683 initiators of DPP-4 inhibitors were included in the GIM and GIMH population, and 5,802 initiators of empagliflozin and 31,940 initiators of DPP-4 inhibitors were included in the GIF and GIFH population. Genital infections were more frequent among females than among males and among initiators of empagliflozin (adjusted IR per 1,000 person-years, 47.23 for GIM; 43.35, GIMH; 79.65, GIF; and 58.82, GIFH) than among initiators of DPP-4 inhibitors (adjusted IR per 1,000 person-years, 11.70 for GIM; 10.72, GIMH; 24.58, GIF; and 17.48, GIFH). A 3-fold to 4-fold increased risk of GI and severe GI was observed among initiators of empagliflozin compared with initiators of DPP 4 inhibitors—adjusted IRR, 4.04 (95% CI, 3.46-4.71) for GIM; 3.24 (95% CI, 2.81-3.74) for GIF; 4.04 (95% CI, 3.44-4.75) for GIMH; and 3.34 (95% CI, 2.83-3.95) for GIFH. The increase in risk of severe GI in males and females initiating empagliflozin compared with initiators of DPP-4 inhibitors was similar to that observed for the GI primary outcome in males and females.

Results were consistent across subgroups and sensitivity analyses. For several subgroups, analyses included a low number of events, especially in Danish Registries, which led to low precision of effect estimates or non-estimable IRRs. In sensitivity analyses, the results when using an intention-to-treat (ITT) analysis and when evaluating recent use tended to be closer to the null.

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	Because of the limitations of the validation process and the low number of events identified for the rare outcomes, the PPVs were in general imprecise. In HIRD, and for the ALI outcomes, the PPVs were especially imprecise, with a high degree of uncertainty around the point estimates. They were very different for the empagliflozin and DPP-4 inhibitor cohorts. This impacted the results of the sensitivity analyses based on those PPVs. Results from the sensitivity analyses including only confirmed events were generally in line with the main results, with occasional exceptions that coincided with extremely wide CIs due to the small number of confirmed events for some outcomes (i.e., ALI1 and AKI in HIRD). The sensitivity analysis using PPVs to correct for potential outcome misclassification also had results generally in line with the main analysis results, with occasional exceptions that coincided with low precision of the estimate in the sensitivity analysis (i.e., ALI1, ALI1S, and ALI2 in HIRD).
Discussion:	The study results need to be interpreted considering potential limitations and biases. Although channelling bias cannot be completely discarded, the study design sought to avoid it by using a new-user design with an active comparator drug (DPP-4 inhibitors), by including all potential confounders and variables associated with the outcome in the propensity score models; by balancing exposure cohorts in all baseline characteristics; and by analysing the potential impact of calendar year in the distribution of baseline confounders, the association of the exposure with the outcome by calendar year, and the effect of calendar year in several propensity score models. Results from this study showed that there was no impact of calendar year in any analysis and that including an interaction term for calendar year in the models did not improve the overlapping of the propensity score distribution curves. Propensity scores were estimated to account for potential confounding, but residual confounding due to unmeasured variables cannot be discarded, especially for the outcome severe complications of UTI. However, results from the quantitative bias analysis showed that residual confounding was

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unlikely to account for most of the decreased relative risk observed for severe complications of UTI or the increased relative risk observed for DKA. For the other outcomes (ALI1, ALI2, AKI, and CKD), the beneficial associations with empagliflozin observed for several of the current study outcomes are compatible with what has previously been described as being potentially due to the effects of SGLT2 inhibitors on body weight, diuresis, blood pressure, alanine aminotransferase (ALT), and estimated glomerular filtration rate (eGFR)—factors that potentially mediate in part the improvement in cardio-renal-metabolic disease outcomes among patients with T2D treated with empagliflozin [P20-02445].

Misclassification of exposure and outcome is a risk in all studies conducted using routinely collected data from automated population-based data sources. Regarding misclassification of exposure, some limitations in this study are shared with all such studies, but the study results did not change when sensitivity analyses assuming longer, alternative definitions of duration of exposure were conducted. The consistency of results using alternative exposure duration windows does not support exposure misclassification.

Outcome misclassification was possible, and the validation process had severe limitations due to the low response rate of GP questionnaires and the unavailability of inpatient laboratory results in CPRD; the low number of events (and the low number of validated events) for some outcomes in all data sources, which impacted the precision of PPVs, especially for the rarest outcomes; and the unavailability of specific test results required for validation (e.g., ketosis measurements for the DKA outcome). Despite those limitations, in most of the sensitivity analyses performed on only validated events or corrected by the PPV, results were in line with the main analysis and with all other sensitivity analyses, with notable exceptions for the less common ALI1 outcome.

For some outcomes, such as ALI1 and DKA, the precision of the adjusted IRRs (as assessed by the width of 95% CIs) in some data sources was low

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	and compatible with both a decreased and an increased risk, especially for some subgroup analyses. In conclusion, these results indicate that use of empagliflozin compared with the use of DPP-4 inhibitors is associated with an increased risk of diabetic ketoacidosis (approximately 2-fold), and genital infections (approximately 4-fold), which are identified risks in the risk management plan and are considered as class effects for SGLT2 inhibitors. Results also indicate that use of empagliflozin compared with the use of DPP-4 inhibitors is associated with a decreased risk of acute liver injury among patients with and without predisposing conditions, decreased risk of acute kidney injury and chronic kidney disease, and decreased risk of severe complications of urinary tract infection, all of which may potentially be explained by the beneficial metabolic effects of empagliflozin. The results were consistent across data sources and across all subgroup and sensitivity analyses, although some variations in the IRRs were observed, which were likely related to the small numbers of events in some analyses.
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