Study Report

P4-C1-004

DARWIN EU® - Characterisation of acute renal outcomes and severe diabetic complications among patients with concomitant use of metformin and iodinated contrast agents

23/03/2026

Version 4.0

Authors: Wanning Wang, Daniel Prieto-Alhambra

Confidential

CONTENTS

Study title	DARWIN EU® - Characterisation of acute renal outcomes and diabetic complications among patients with concomitant use of metformin and iodinated contrast agents
Study report version	V4.0
Date	23/03/2026
EUPAS number	EUPAS1000000662
Active substance	Metformin, iodinated contrast agents (ICA)
Medicinal product	N/A
Research question and objectives	1. To characterise patients with type 2 diabetes initiating treatment of metformin in terms of: a. Demographics (age, sex) b. Recorded comorbidities c. Recorded duration from first diabetes diagnosis d. Previous procedures with ICA, including phenotyping e. Chronic kidney disease (CKD) stage (most recent in past year), including phenotyping 2. To characterise patients with type 2 diabetes with a first procedure requiring ICA during metformin use in terms of: a. Demographics (age, sex) b. Comorbidities c. Recorded duration from first diabetes diagnosis d. CKD stage e. ICA type f. Time from metformin initiation to first procedure requiring ICA 3. To quantify the occurrence of renal dysfunction and of acute diabetes decompensation among patients with type 2 diabetes undergoing a procedure requiring ICA during metformin use, specifically: a. Acute kidney injury (AKI), including phenotyping b. Lactic acidosis c. Diabetic ketoacidosis d. Change in eGFR and CKD status before and after date of first procedure requiring ICA Objective 3 was the primary objective of the study, while objectives 1 and 2 were secondary objectives.
Countries of study	Denmark, Finland, Spain, the United Kingdom
Authors	W. Wang (w.wang@darwin-eu.org) D. Prieto-Alhambra (d.prietoalhambra@darwin-eu.org)

LIST OF ABBREVIATIONS

Acronyms/term	Description
AKI	Acute Kidney Injury
CDM	Common Data Model
CHMP	Committee for Medicinal Products for Human Use
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disorder
CPRD GOLD	Clinical Practice Research Datalink GOLD
DARWIN EU	Data Analysis and Real-World Interrogation Network
DK-DHR	Danish Data Health Registries
eGFR	Estimated Glomerular Filtration Rate
EHR	Electronic Health Records
EMA	European Medicines Agency
EU	European Union
FinOMOP-THL	Finnish Care Register for Health Care
GERD	Gastroesophageal Reflux Disease
GP	General Practitioner
HIV	Human Immunodeficiency Virus
ICA	Iodinated Contrast Agent
ICD-10	International Classification of Diseases 10th revision
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
PC	Primary Care
PI	Product Information
PRAC	Pharmacovigilance Risk Assessment Committee
pCr	Plasma Creatine
PSUSA	Periodic safety update report single assessments
RWD	Real-world Data
SC	Secondary Care
SIDIAP	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària
THL	The Finnish Institute for Health and Welfare
UK	The United Kingdom

1. TITLE

DARWIN EU® - Characterisation of acute renal outcomes and diabetic complications among patients with concomitant use of metformin and iodinated contrast agents

2. DESCRIPTION OF THE STUDY TEAM

Study team role	Names	Organisation
Principal Investigator	Wanning Wang	University of Oxford
Data Scientist	Nuria Mercade Besora Edward Burn	University of Oxford University of Oxford
Epidemiologist	Daniel Prieto Alhambra	University of Oxford
Clinical Domain Expert	Albert Prats Uribe George Corby Anna Saura Lazaro	University of Oxford University of Oxford University of Oxford
Study Manager	Natasha Yefimenko	Erasmus MC
Data source	**Names**	**Data Partner Organisation***
DK-DHR	Elvira Bräuner Susanne Bruun	Danish Medicines Agency
FinOMOP- THL	Gustav Klingstedt Tiina Wahlfors Toni Lehtonen	The Finnish Institute for Health and Welfare
SIDIAP	Agustina Giuliodori Picco Elena Roel Herranz Laura Granés González Irene López Sánchez Anna Palomar-Cros	IDIAPJGol
CPRD GOLD	Marta Pineda Moncusí Antonella Delmestri	University of Oxford

*Data partners do not have an investigator role. Data partners execute code at their data source, review, and approve their results.

3. ABSTRACT

Title

DARWIN EU® - Characterisation of acute renal outcomes and diabetic complications among patients with concomitant use of metformin and iodinated contrast agents (ICAs)

Rationale and background

Art.31 Committee for Medicinal Products for Human Use (CHMP) referral in 2016 on metformin and use in patients with reduced kidney function led to product information (PI) updates, including introduction of a warning on an interaction with concomitant use with iodinated agents for patients undergoing imaging procedures.

Based on the evidence reviewed in the Periodic Safety Update Report Single Assessment (PSUSA) in the December 2024 meeting, it was considered premature to delete the warning and the interaction in the metformin PIs at this stage. Pharmacovigilance Risk Assessment Committee (PRAC) suggested the possibility to conduct a real-world data (RWD) study to gather more data on this specific issue and to better understand if further regulatory action would be deemed necessary.

Research question and objectives

1. To characterise patients with type 2 diabetes initiating treatment of metformin in terms of:
    a. Demographics (age, sex)
    b. Recorded comorbidities
    c. Recorded duration from first diabetes diagnosis until metformin initiation
    d. Previous procedures with ICA, including phenotyping
    e. Chronic Kidney Disease (CKD) stage (most recent in past year), including phenotyping
2. To characterise patients with type 2 diabetes with a first procedure requiring ICA with ongoing metformin use in terms of:
    a. Demographics (age, sex)
    b. Comorbidities
    c. Recorded duration from first diabetes diagnosis until first procedure requiring ICA
    d. CKD stage
    e. ICA type
    f. Time from metformin initiation to first procedure requiring ICA
3. To quantify the occurrence of renal dysfunction and of acute diabetes decompensation among patients with type 2 diabetes with a first procedure requiring ICA during metformin use specifically:
    a. Acute Kidney Injury (AKI), including phenotyping
    b. Lactic acidosis
    c. Diabetic ketoacidosis
    d. Change in estimated glomerular filtration rate (eGFR) and CKD status before and after date of first procedure requiring ICA.

Objective 3 was the primary objective of the study, while objectives 1 and 2 were secondary objectives.

Methods

Study design

New user cohort study

Population

Two cohorts:

1. Metformin users (cohort 1): new users of metformin between 01/01/2014 and latest date available, with a diagnosis of diabetes, and at least 365 days of history prior to the date of their first metformin prescription and no prior use of metformin. Index date was the date of first prescription of metformin.
2. Metformin+ ICA users (cohort 2): first procedure requiring an ICA between 01/01/2014 and latest date available, with metformin initiation during the study period, ongoing metformin use with metformin initiation prior to ICA procedure, previous diagnosis of diabetes, and 365 days of prior history before metformin initiation. ICA new use population was a subset of the metformin new users (Cohort 1). Index date was the date of first procedure requiring ICA where the above conditions applied.

We excluded patients with a record of AKI, ketoacidosis, or diabetic acidosis within a year of index date.

Variables

Exposures:

ICA, metformin

Outcomes:

- AKI
- Lactic acidosis
- Diabetic ketoacidosis
- Change in eGFR and CKD status before and after date of first procedure requiring ICA.

Covariates for characterisation:

- Demographics (age, sex)
- Comorbidities: Anxiety, asthma, CKD, chronic liver disease, chronic obstructive pulmonary disorder (COPD), dementia, gastroesophageal reflux disease (GERD), heart failure, human immunodeficiency virus (HIV), hypertension, hypothyroidism, inflammatory bowel disease, malignant neoplastic disease, myocardial infarction, osteoporosis, pneumonia, rheumatoid arthritis, stroke, venous thromboembolism
- Duration of diabetes (days from initial diagnosis of type 2 diabetes to index date)
- Previous use of ICA at metformin initiation in the cohort of metformin users
- CKD stage
- ICA type
- Time from metformin initiation to first procedure requiring ICA

Objective 3: Survival analyses will be stratified by

- ICA indication/type
- CKD stage (1–5)

Data sources

1. Denmark: Danish Data Health Registries (DK-DHR)
2. Finland: Finnish Care Register for Health Care (FinOMOP-THL)
3. Spain: The Information System for Research on Primary Care (SIDIAP)
4. The United Kingdom: Clinical Practice Research Datalink GOLD (CPRD GOLD)

Statistical analysis

Characterisation was done for both new metformin users (index date = date of first prescription) and metformin users with a first procedure requiring ICA during ongoing metformin use (index date = date of first procedure requiring an ICA). Both cohorts were characterised in terms of patient demographics, comorbidities, time since diabetes diagnosis, and CKD stage. For new metformin users, previous use of ICA was assessed, while for metformin users with a first procedure requiring ICA, the ICA type and time from metformin initiation until ICA was assessed.

We estimated Kaplan-Meier survival functions to describe the probability of outcome occurrence and median survival to outcomes of interests, specifically AKI, lactic acidosis, diabetic ketoacidosis among patients with type 2 diabetes with a first procedure requiring ICA during metformin use stratified by CKD stage, and ICA type. As an exploratory analysis for outcomes of interest, we described change in eGFR and CKD status before and after date of first procedure requiring ICA.

For all analyses, a minimum cell counts of 5 was used when reporting results, with any smaller counts noted as <5.

Results

The size of the metformin cohort ranged from 32,302 individuals in DK-DHR to 151,422 in SIDIAP, whereas the metformin+ICA cohort was substantially smaller, with 231 individuals in CPRD GOLD, 529 in DK-DHR, 526 in FinOMOP-THL, and 9,795 in SIDIAP. Individuals in the metformin cohort were slightly younger in age, with a median age ranging from 62 to 64, compared to the metformin+ICA cohort, with median age ranging from 62 to 71 years of age.

Among the metformin+ICA cohorts there were 747 AKI events and 44 ketoacidosis events in SIDIAP. The cumulative incidence of AKI from an ICA procedure until the end of follow up was 3% in CPRD GOLD, 1% in DK-DHR, 7.7% in SIDIAP, and FinOMOP-THL had <5 events. The cumulative incidence of AKI in SIDIAP differed across different CKD stages, with stage 1 having the lowest (3.6%) and stage 4 the highest cumulative incidence of AKI (26.5%). Among the metformin+ICA cohort, there were 44 individuals recorded to have a diagnosis of ketoacidosis in SIDIAP and no ketoacidosis recording was reported in the other data sources. Lactic acidosis events were not recorded in any of the data sources and cohorts. When evaluating changes in eGFR for metformin users before and after ICA procedure, the median change in eGFR measurement was 0.0 in both CPRD GOLD (range -88.00 to 72.00) and SIDIAP (-30.00 to 35.00). In addition, there were minor changes in CKD stages captured from recordings and eGFR measurements before and after ICA procedure. For CKD stages after ICA procedure, there were changes in the different categories: 'Missing', higher and lower stages, in SIDIAP, whereas CKD stages were relatively stable after ICA procedure in CPRD GOLD. CKD stage could not be characterised for DK-DHR and FinOMOP-THL due to lack of eGFR measurements.

In a post-hoc analysis which included a cohort definition for metformin users where type 2 diabetes was captured on index date , DK-DHR incurred more individuals in their cohort and 11 AKI events. However, there were no records of ketoacidosis or lactic acidosis, and there were no major trends in changes in eGFR measurements or CKD stage.

Discussion

Our study showed that there were low numbers of metformin users with an ICA procedure in three of the four contributing data sources: DK-DHR, FinOMOP-THL, and CPRD GOLD. The low number of identified records of ICA among metformin users could be due to lack of hospital records in CPRD GOLD and due to lack of granularity in source coding vocabularies in DK-DHR and FinOMOP-THL. Overall, metformin users who underwent ICA procedures were older and had more comorbidities compared to the overall metformin user cohorts. Additionally, there were a low number of metformin users who underwent ICA procedures with AKI and no lactic acidosis and ketoacidosis recorded in DK-DHR and FinOMOP-THL. Patients in the metformin+ICA cohorts had 44 events of ketoacidosis in SIDIAP with cumulative incidence of AKI estimated at 3% in CPRD GOLD, 7.7% in SIDIAP, and 1% in DK-DHR.

Post-hoc analyses in DK-DHR to include a cohort definition for metformin users where type 2 diabetes was captured on index date and an additional eGFR measurement code resulted in more individuals in both the metformin and ICA cohorts. However, AKI events were still low and there were no events of ketoacidosis or lactic acidosis.

The regulatory motivation for this study was to assess whether existing real-world data in the DARWIN EU® network could be useful to evaluate compliance with the SmPC recommendation to temporarily interrupt metformin treatment around procedures involving ICA, and/or to compare safety outcomes according to whether this recommendation is followed. The limited numbers of patients eligible for such analyses in 3 of the 4 proposed data sources, together with the known lack of completeness and granularity on temporary and short-term drug discontinuation make it unlikely that further research using these data will be useful to answer the aforementioned regulatory objectives.

4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Study deliverable	Timelines (planned)	Timelines (actual)
Final Study Protocol	To be confirmed by EMA	14 July 2025
Creation of Analytical code	July 2025	July – August 2025
Execution of Analytical Code on the data	August 2025	August – September 2025
Draft Study Report	September 2025	November 2025
Final Study Report		

6. RATIONALE AND BACKGROUND

Art.31 Committee for Medicinal Products for Human Use (CHMP) referral in 2016 on metformin and use in patients with reduced kidney function led to product information (PI) updates, including introduction of a warning and an interaction with concomitant use with iodinated agents for patients undergoing imaging procedures.

Based on the evidence reviewed in the Periodic Safety Update Report Single Assessment (PSUSA) in December 2024, it was considered premature to delete the warning and interaction in the metformin PIs at this stage. The Pharmacovigilance Risk Assessment Committee (PRAC) suggested the possibility to conduct a real-world data (RWD) study to gather more data on this specific issue.

The resulting study was designed within 4 data partners in the DARWIN EU® data network to determine the number of individuals who use metformin and undergo an Iodinated Contrast Agent (ICA) procedure; to describe their characteristics compared to overall metformin users; and to calculate how many people experience renal dysfunction after ICA. Understanding the availability of RWD within the DARWIN EU® network will inform the feasibility of a safety study to understand the potential association between concomitant use of metformin and ICA and renal dysfunction.

7. RESEARCH QUESTION AND OBJECTIVES

Description of the proposed objectives to be achieved in the study (**Table 1**).

Table 1. Primary and secondary research questions and objective.

A. Objective 1 (secondary)

Objective:	To characterise patients with type 2 diabetes initiating treatment of metformin in terms of demographics, comorbidities, duration of diabetes, previous use of ICA, CKD stage, including phenotyping of ICA and CKD stage.
Hypothesis:	N/A
Population *(mention key inclusion-exclusion criteria):*	Metformin users: new users of metformin identified between 01/01/2014 and latest date available, with a diagnosis of diabetes and at least 365 days of history prior to the date of their first metformin prescription and no prior use of metformin. We excluded patients with a record of AKI, ketoacidosis, or diabetic acidosis within a year prior to (date of first prescription of metformin).

Exposure:	Metformin
Comparator:	N/A
Outcome:	N/A
Time *(when follow up begins and ends):*	Follow-up started on the date of metformin (index date). Comorbidities, previous use of ICA, and CKD stage was evaluated based on most recent records 365 days prior to index date. Demographics and duration of diabetes was evaluated on index date.
Setting:	Primary care records and nationwide health registries from: DK-DHR [Denmark], FinOMOP-THL [Finland], SIDIAP linked to hospital discharge records [Spain], CPRD GOLD [the United Kingdom].
Main measure of effect:	We described user demographic characteristics including age, sex, and comorbidities. We also described the duration of diabetes and CKD stage and described the proportion with previous use of ICA. For phenotyping of ICA, we described the number of users with an occurrence of ICA procedures, number of users included in the broad and narrow cohorts of ICA procedures and their overlap, proportion of users with specific types of ICA procedures, and number of users in the ICA procedure cohorts was provided for each database. For phenotyping of CKD stage, we described number of users with a record of CKD stage or eGFR measurements.

B. Objective 2 (secondary)

Objective:	To characterise patients with type 2 diabetes with first use of ICA during ongoing metformin use in terms of demographics, comorbidities, duration of diabetes, CKD stage, ICA type, and time from metformin initiation to first procedure requiring ICA.
Hypothesis:	N/A
Population *(mention key inclusion-exclusion criteria):*	Metformin+ ICA users: first procedure requiring an ICA between 01/01/2014 and latest date available, with first use of metformin during the study period, ongoing metformin use with metformin initiation prior to ICA procedure, previous diagnosis of diabetes, and 365 days of prior history before metformin initiation. We excluded patients with a record of AKI, ketoacidosis, or diabetic acidosis within a year prior to date of first procedure requiring an ICA.
Exposure:	Metformin, ICA
Comparator:	N/A
Outcome:	N/A
Time *(when follow up begins and ends):*	Follow-up started on the date of first procedure requiring ICA (index date). Comorbidities, previous use of contrast, and CKD stage was evaluated based on most recent records 365 days prior to index date. Demographics, duration of diabetes, ICA type, and time from metformin initiation was evaluated on index date.
Setting:	Primary care records and nationwide health registries from DK-DHR [Denmark], FinOMOP-THL [Finland], SIDIAP linked to hospital discharge records [Spain], CPRD GOLD [the United Kingdom].
Main measure of effect:	We described demographic characteristics including age, sex, and comorbidities. We described the type of ICA and time from metformin initiation to first procedure requiring ICA.

C. Objective 3 (primary)

Objective:	To quantify the occurrence of renal dysfunction and of acute diabetes decompensation among patients with type 2 diabetes with a first procedure requiring ICA during ongoing metformin use.
Hypothesis:	N/A
Population *(mention key inclusion-exclusion criteria):*	Metformin+ ICA users: first procedure requiring an ICA between 01/01/2014 and latest date available, with first use of metformin during the study period, ongoing metformin use with metformin initiation prior to ICA procedure, previous diagnosis of diabetes, and 365 days of prior history before metformin initiation. We excluded patients with a record of AKI, ketoacidosis, or diabetic acidosis within a year prior to first procedure requiring ICA.
Exposure:	Metformin, ICA
Comparator:	N/A
Outcomes:	1. AKI, including phenotyping 2. Lactic acidosis 3. Diabetic ketoacidosis Change in eGFR and CKD status before and after date of first procedure requiring ICA
Time *(when follow up begins and ends):*	Follow up will start at index date (first procedure requiring ICA whilst on metformin therapy) until end of the study period, death, occurrence of the outcome, or data availability, whichever comes first. Patients were censored at metformin discontinuation. Change in CKD and eGFR status from ICA initiation was evaluated at the most recent record within 365 days prior to ICA initiation and the earliest record within 365 days after ICA initiation.
Setting:	Primary care records and nationwide health registries from DK-DHR [Denmark], FinOMOP-THL [Finland], SIDIAP linked to hospital discharge records [Spain], CPRD GOLD [the United Kingdom].
Main measure of effect:	Kaplan-Meier curves to estimate probability of outcome occurrence and median survival for each of the outcomes of interest, stratified by CKD stage and ICA type. For phenotyping we described code counts of AKI diagnoses using conditions and counts using eGFR measurements. For change in CKD and eGFR status from ICA initiation, we described the measurements at the two time points, the proportion with a change of CKD status of one stage or more, and the median change in eGFR measurement at these time points.

AKI = Acute Kidney Injury; ICA = Iodinated Contrast Agent; CKD = Chronic Kidney Disease; DK-DHR = Danish Data Health Registries; FinOMOP-THL = Finnish Care Register for Health Care; SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària; CPRD GOLD = Clinical Practice Research Datalink GOLD; eGFR = Estimated Glomerular Filtration Rate.

8. RESEARCH METHOD

8.1. Study design

Retrospective cohort studies were conducted using routinely collected health data from 4 data sources. **Table 2** describes the study types and related study designs. The study comprised of two study designs:

1. A new user cohort study among patients with type 2 diabetes initiating metformin (Objective 1)
2. A cohort study among patients with type 2 diabetes with a first procedure requiring ICA during ongoing metformin use (Objective 2, 3)

Table 2. Description of study types and related study design.

Study type	Study design	Study classification
Patient-level characterisation	Cohort analysis	Off the shelf

8.2. Follow-up

For characterisation among metformin users, variables of interest were evaluated at date of first prescription of metformin or within 365 days prior to index date.

For characterisation among new users of ICA during ongoing metformin use, variables of interest were evaluated at date of first procedure requiring ICA or within 365 days prior to index date.

For survival analyses among patients' first procedure requiring ICA during ongoing metformin use, follow up started at first procedure requiring ICA and patients were followed until loss to follow up, lack of data availability, occurrence of outcome, death, or end of study period, whichever came first. Patients were censored at metformin discontinuation. Change in CKD and eGFR status from ICA initiation was evaluated at the most recent record within 365 days prior to ICA initiation and the earliest record within 365 days after undergoing ICA. **Table S1** describes the index date for each cohort.

8.3. Study population with inclusion and exclusion criteria

Our study consisted of two study populations:

1. Cohort 1: Patients with type 2 diabetes initiating metformin. Patients were included if they satisfied the following criteria:
    a. First prescription of metformin (index date) between 1st January 2014 and latest date available
    b. Diagnosis of type 2 diabetes any time before index date
    c. 365 days of prior history before index date
2. Cohort 2: Patients with type 2 diabetes on metformin undergoing their first procedure requiring ICA. Patients were included if they satisfied the following criteria:
    a. First procedure requiring ICA (index date) between 1st January 2014 and latest date available
    b. First prescription of metformin between 1st January 2014 and latest date available
    c. Metformin use on index date
    d. Metformin initiation prior to first procedure requiring ICA
    e. Diagnosis of type 2 diabetes any time before first prescription of metformin
    f. 365 days of prior history before index date

Cohort 2 was a subset of Cohort 1.

Patients were excluded if they had an outcome of interest (AKI, lactic acidosis, diabetic ketoacidosis) within 365 days of index date (date of first prescription of metformin/date of first procedure requiring ICA depending on cohort of interest) or if metformin was discontinued. **Figure 1** depicts the two study populations with the criteria applied for survival analyses follow up.

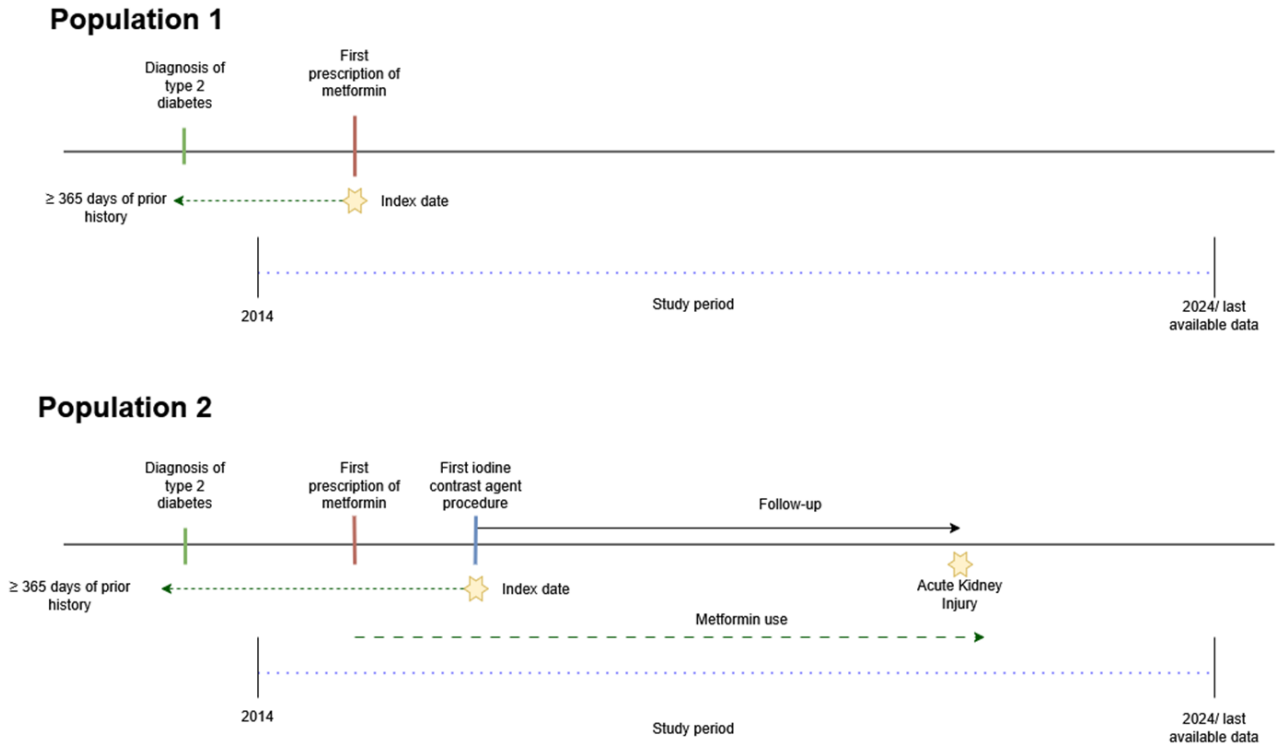

Figure 1. Graphical description of study populations for survival analyses follow up.

The operational definitions of the inclusion and exclusion criteria are presented by means of **Table S2** and **Table S3**, respectively.

8.4. Study setting and data sources

This study was conducted using routinely collected data from 4 data sources from 4 European countries. All data sources were previously mapped to the Observational Medical Outcomes Partnership Common Data Model (OMOP CDM).

1. Denmark: Danish Data Health Registries (DK-DHR)
2. Finland: Finnish Care Register for Health Care (FinOMOP-THL)
3. Spain: The Information System for Research on Primary Care (SIDIAP)
4. The United Kingdom: Clinical Practice Research Datalink GOLD (CPRD GOLD)

Information on data sources planned to be used with a justification for their choice in terms of ability to capture the relevant data is described in **Table S4**.

8.5. Study period

The study period was from the 1st of January 2014 until the latest date of data availability of the respective data sources.

8.6. Variables

8.6.1. Exposure

The exposure of interest was procedures requiring ICA. A list of relevant codes is attached in a supplementary document (ICA_codelist.csv). We specifically searched for types of imaging procedures: angiography, CT angiography, CT urography, urography, CT enterography, enterography, cardiac CT, angiogram, fluoroscopy, perfusion, myelography, venography.

For both populations of interest, metformin use was required for study entry. Metformin was monotherapy or in combination with other antidiabetic drugs. The ATC code for metformin is A10BA02.

The assessment of exposure and the operational definition of exposure is described in **Table S5**.

8.6.2. Outcome

The outcomes of the study were related to acute renal outcomes and acute diabetic complications.

We quantified the following outcomes among patients who had a first procedure requiring ICA during ongoing metformin use:

- AKI
- Lactic acidosis
- Diabetic ketoacidosis
- Change in eGFR or CKD status before and after date of first procedure requiring ICA

The study outcomes are described conceptually, and the context or rationale for the choices are provided in this section. The operational definition of the outcomes is presented in **Table S6**.

8.7. Study size

No sample size was calculated, as this was a descriptive study with no hypothesis testing.

8.7.1. Covariates, including confounders, effect modifiers, intercurrent events, and other variables

Objective 1: Characterisation of patients with type 2 diabetes initiating treatment of metformin in terms of:

1. Demographics (age, sex)
2. Comorbidities: Anxiety, asthma, CKD, chronic liver disease, chronic obstructive pulmonary disorder (COPD), dementia, gastroesophageal reflux disease (GERD), heart failure, human immunodeficiency virus (HIV), hypertension, hypothyroidism, inflammatory bowel disease, malignant neoplastic disease, myocardial infarction, osteoporosis, pneumonia, rheumatoid arthritis, stroke, venous thromboembolism
3. Duration of diabetes (days from initial diagnosis of type 2 diabetes to index date)
4. Previous use of ICA
5. CKD stage (1–5)

Objective 2: Characterisation of patients with type 2 diabetes with first use of ICA during ongoing metformin use in terms of:

1. Demographics (age, sex)
2. Comorbidities: Anxiety, asthma, CKD, chronic liver disease, chronic obstructive pulmonary disorder (COPD), dementia, gastroesophageal reflux disease (GERD), heart failure, human immunodeficiency virus (HIV), hypertension, hypothyroidism, inflammatory bowel disease, malignant neoplastic disease,

myocardial infarction, osteoporosis, pneumonia, rheumatoid arthritis, stroke, venous thromboembolism

3. Duration of diabetes (days from initial diagnosis of type 2 diabetes to index date)
4. CKD stage (1–5)
5. ICA type
6. Time from metformin initiation to first procedure requiring ICA

Objectives 3: Survival analyses were stratified by:

1. ICA type
2. CKD stage (1–5)

The study covariates are described conceptually, and the context or rationale for the choices are provided in this section. The operational definition of the covariates is described in the **Table S7**.

8.8. Data transformation

Analyses were conducted separately for each data source. Before study initiation, test runs of the analyses were performed on a subset of the data sources and quality control checks were performed. Once all the tests passed (see **Annex III**), the final study codes package was released in the version-controlled Study Repository for execution against all the participating data sources.

The data partners locally executed the analytics against the OMOP CDM in R Studio and reviewed and approved the, by default, aggregated results.

The study results of all data sources were checked, after which they were made available to the team, and the dissemination phase started. All results were locked and timestamped for reproducibility and transparency.

8.9. Statistical methods

Main summary measures

8.9.1. Main statistical methods

This section describes the details of the analysis approach and rationale for the choice of analysis, with reference to the D1.3.8.1 Draft Catalogue of Data Analysis, which describes the type of analysis in function of the study type. Description of type of analysis based on study type is provided in **Table 3**.

Table 3. Description of study types and type of analysis

Study type	Study classification	Type of analysis
Patient-level characterisation	Off-the-shelf	- Patient-level characteristics - Phenotyping and characterisation of ICA use - Phenotyping of AKI and CKD - Survival analyses

R-packages

We used the R package *CohortCharacteristics* to describe patient-level characterisation, *IncidencePrevalence* package for the population-level estimation of drug utilisation, and the *PhenotypeR* package to phenotype and characterise ICA use in the general population.

Drug exposure calculations

Drug eras for each metformin user were defined as follows: Exposure starts at date of the first prescription, e.g., the index date the person entered the cohort. For each prescription, the estimated duration of use was retrieved from the drug exposure table in the CDM. Subsequent prescriptions were combined into continuous exposed episodes (drug eras) using the following specifications. Two drug eras were merged into one continuous drug era if the distance in days between end of the first era and start of the second era is ≤30 days. The time between the two joined eras were considered as exposed by the first era as shown in Figure 2 **Figure 2**.

Gap era joint mode	Schematics	Dose in between	Cumulative dose	Cumulative time
"first"		d_1	$d_1 \cdot (x_1 + x_{12}) + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"second"		d_2	$d_1 \cdot x_1 + d_2 \cdot (x_2 + x_{12})$	$x_1 + x_{12} + x_2$
"zero"		0	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"join"		NA	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_2$

Figure 2: Drug era construction, taking into consideration gap variations between subsequent exposures.

If two eras overlap, the overlap time was considered exposed by the first era (**Figure 3**). No time was added at the end of the combined drug era to account for the overlap. If two exposures start at the same date, the overlapping period was considered exposed to both.

Overlap mode	Schematics	Dose overlap
"first"		d_1
"second"		d_2
"both"		$d_1 + d_2$
"maximum"		$\max(d_1, d_2)$

Figure 3. Drug era construction, taking into consideration doses between overlapping exposures.

New user cohorts

New users were selected based on their first prescription of the respective drug or procedure of interest after the start of the study and/or in a pre-defined time window. For each patient, at least 365 days of data visibility was required prior to that prescription/procedure. New users were required to not have been exposed to the drug of interest any time prior the current prescription. If the index day does not fulfil the exposure washout criteria the whole exposure is eliminated.

8.9.1.1 Methods to derive parameters of interest

Calendar time

Calendar time was based on the calendar year of the index prescription.

Age

Age at index date was calculated using January 1st of the year of birth as proxy for the actual birthday. The following age groups were used for stratification: <40, 40–59, 60–79, 80 and above years old.

Characterisation of patient-level features (comorbidities)

We reported frequency of comorbidities that were recorded within 365 days prior to index date.

Duration of diabetes

Duration of diabetes was calculated, where applicable, as years between the date of diabetes diagnosis and the index date.

Survival Analyses

To obtain Kaplan-Meier plots, patients were followed from index date to evaluate probability of outcome occurrence and median survival to outcomes of interest. Patients were censored if before the end of study period, they were lost to follow up, lacked data availability, outcome occurrence, or metformin was discontinued.

8.9.1.2 Methods planned to obtain point estimates with confidence intervals of measures of occurrence

Patient-level characterisation study

New drug user patient-level characteristics on/before index date

For each concept extracted before/at index date, the number of persons (N, %) with a record within the pre-specified time windows was provided.

Comorbidities

The number of persons (N, %) with a record of comorbidities was provided. If a person had a record of more than one specific comorbidity, that person was included in both specific indication groups separately.

Phenotyping and characterisation of ICA

The code counts of ICA procedures, counts of broad and narrow cohorts of ICA procedures and their overlap, proportion of ICA procedure type, and frequency of ICA procedure cohorts was provided for each data source.

Phenotyping of CKD and AKI

As per the European Medicines Agency (EMA) guidelines on the clinical investigation of medicinal products to prevent development/slow progression of chronic renal insufficiency, the stages of CKD are as follows: the stages 1 and 2 are defined by the presence of markers of renal damage and distinguished from each other by the absence (eGFR >90 ml/min/1.73m2, or stage 1) or presence (eGFR 60–89 ml/min/1.73m2, or stage 2) of mildly reduced eGFR. Stages 3 to 5 are based on the level of eGFR: 30–59 ml/min/1.73m2, or stage 3, 15–29ml/min/1.73m2, or stage 4; and <15 ml/min/1.73m2, or stage 5. Dialysis stage is noted as Stage 5D [1].

Survival Analyses

Kaplan-Meier curves for outcomes of interest were calculated for patients who had a first procedure requiring ICA during ongoing metformin use stratified by CKD stage and ICA type. Kaplan-Meier curves were used to estimate probability of outcome occurrence and median time from day of ICA procedure to outcome occurrence (where applicable).

Change in eGFR/CKD status

As an exploratory analysis, we described the change in eGFR and CKD status before and after first procedure requiring ICA. This was evaluated at the most recent record within 365 days prior to ICA initiation and the earliest record within 365 days after ICA initiation. We described the measurements at the two time points, the proportion with a change of CKD status of one stage or more, and the median change in eGFR measurement at these time points.

8.9.2. Missing values

Missing values for eGFR and CKD status are reporting as “Missing” in the results.

8.9.3. Sensitivity analysis

No sensitivity analyses were performed.

8.10. Deviations from the protocol

DK-DHR results were reported with a new cohort definition where inclusion criteria for prior type 2 diabetes included index date (-inf to 0) as well as an additional eGFR measurement code. These post-hoc analyses results were reported in a separate section: **9.3. Post-Hoc analyses**.

9. RESULTS

The full set of results for this study is available through an interactive web-application ShinyApp at EUPAS1000000662.

Note that for phenotyping, we created two cohorts for ICA based on a broad (excluding codes for procedures that with a high degree of certainty do not use ICA) and narrow (only including codes for procedures that with a high degree of plausibility use ICA). In this report we will focus on the broad definition, results from both definitions can be found in the Shiny App.

9.1. Participants

Based on the inclusion criteria, individuals in the metformin cohort and metformin+ICA cohorts are provided in **Table 4**. In CPRD GOLD, 80,404 individuals were included in the metformin cohort, with 232 individuals in the further subgroup of metformin+ICA users. In DK-DHR (metformin cohort: 32,302 individuals; metformin+ICA cohort: 529 individuals) and FinOMOP-THL (metformin cohort: 119,653 individuals; metformin+ICA cohort: 526) cohort population sizes were similar. For SIDIAP, the metformin cohort was largest with 151,422 individuals, and the metformin+ICA cohort was much larger than in all other data sources with 9,795 participants.

Table 4. Summary of study participants for metformin and ICA cohorts for each data source.

Variable name	CDM name			
	DK-DHR	FinOMOP-THL	SIDIAP	CPRD GOLD
Metformin cohort	32,302	119,653	151,422	80,404
Metformin+ ICA cohort	529	526	9,795	231

CPRD GOLD=Clinical Practice Research Datalink (CPRD) GOLD; DK-DHR=Danish Data Health Registries; FinOMOP-THL= Finnish Care Register for Health Care; SIDIAP=The Information System for Research on Primary Care

Descriptive data

9.2. Main results

9.2.1. Patient Characterisation

Patient characteristics in the metformin cohort were consistent across the data sources of DK-DHR, IPCI, SIDIAP and CPRD GOLD, as described in **Table 5**. The median [IQR] age of the metformin users ranged from 62 [51,73] in DK-DHR to 65 [55,74] in SIDIAP, and the proportion of males from 53% in FinOMOP-THL to 58% in DK-DHR. The most commonly recorded comorbidity was hypertension (ranged 4% in CPRD GOLD to 31% in DK-DHR). Other common comorbidities included asthma (9% in DK-DHR and 5% in FinOMOP-THL) and malignant neoplastic disease (4% in FinOMOP-THL and SIDIAP). None of the metformin users had ICA procedures during the year before metformin initiation (min and max was 0). The median time since diabetes diagnosis ranged from 430 (IQR) days in CPRD GOLD to 1102 (IQR) days in SIDIAP.

CKD staging could not be described for metformin user in DK-DHR and FinOMOP-THL, with almost 100% missing data. In CPRD GOLD and SIDIAP, prevalence of CKD stage 1 (CPRD GOLD: 14%, SIDIAP: 31%) and stage 2 (CPRD GOLD: 51%, SIDIAP: 33%) in metformin users was high. Among metformin users, CKD stages 3, 4 and 5 had a lower prevalence, with CKD stage 3 prevalence estimated at 13% in CPRD GOLD and 8% in SIDIAP, CKD stage 4 and 5 both less than 1% in both data sources.

Table 5. Baseline characteristics of patients in the metformin cohort.

Variable name	Variable level	Estimate name	CDM name			
			DK-DHR	FinOMOP-THL	SIDIAP	CPRD GOLD
Metformin cohort		N	32,302	119,653	151,422	80,404
Age	-	Median [Q25 – Q75]	62 [51 – 73]	64 [54 – 73]	65 [55 – 74]	62 [52 – 71]
Sex	Female	N (%)	13,700 (42.41%)	56,663 (47.36%)	65,158 (43.03%)	34,400 (42.78%)
CKD stage	Stage 1	N (%)	10 (0.03%)	<5	46,270 (30.56%)	11,616 (14.45%)
	Stage 2	N (%)	20 (0.06%)	14 (0.01%	50,569 (33.40%)	40,759 (50.69%)
	Stage 3	N (%)	77 (0.24%)	27 (0.02%)	11,713 (7.74%)	10,322 (12.84%)
	Stage 4	N (%)	18 (0.06%)	<5	154 (0.10%)	48 (0.06%)
	Stage 5	N (%)	35 (0.11%)	20 (0.02%)	83 (0.05%)	128 (0.16%)
	Missing	N (%)	32,142 (99.50%)	119,589 (99.95%)	42,633 (28.16%)	17,531 (21.80%)
Comorbidities (0 to 365 days prior)	Anxiety	N (%)	1,442 (4.46%)	3,803 (3.18%)	7,345 (4.85%)	1,820 (2.26%)
	Asthma	N (%)	2,981 (9.23%)	6,193 (5.18%)	2,125 (1.40%)	1,207 (1.50%)

Variable name	Variable level	Estimate name	CDM name			
			DK-DHR	FinOMOP-THL	SIDIAP	CPRD GOLD
	Chronic kidney disease	N (%)	422 (1.31%)	523 (0.44%)	4,820 (3.18%)	1,053 (1.31%)
	Chronic liver disease	N (%)	360 (1.11%)	525 (0.44%)	1,078 (0.71%)	150 (0.19%)
	COPD	N (%)	2,520 (7.80%)	2,674 (2.23%)	4,942 (3.26%)	1,568 (1.95%)
	Dementia	N (%)	422 (1.31%)	2,340 (1.96%)	1,756 (1.16%)	270 (0.34%)
	GERD	N (%)	136 (0.42%)	774 (0.65%)	2,862 (1.89%)	331 (0.41%)
	Heart failure	N (%)	2,223 (6.88%)	4,087 (3.42%)	4,810 (3.18%)	602 (0.75%)
	HIV	N (%)	71 (0.22%)	124 (0.10%)	142 (0.09%)	<5
	Hypertension	N (%)	10,065 (31.16%)	35,830 (29.94%)	21,364 (14.11%)	3,402 (4.23%)
	Hypothyroidism	N (%)	1,754 (5.43%)	3,985 (3.33%)	3,978 (2.63%)	584 (0.73%)
	Inflammatory bowel disease	N (%)	359 (1.11%)	969 (0.81%)	231 (0.15%)	84 (0.10%)
	Malignant neoplastic disease	N (%)	2,198 (6.80%)	5,215 (4.36%)	6,309 (4.17%)	1,288 (1.60%)
	Myocardial infarction	N (%)	884 (2.74%)	2,397 (2.00%)	2,654 (1.75%)	833 (1.04%)
	Osteoporosis	N (%)	1,336 (4.14%)	618 (0.52%)	1,855 (1.23%)	189 (0.24%)
	Pneumonia	N (%)	3,365 (10.42%)	2,841 (2.37%)	3,963 (2.62%)	509 (0.63%)
	Renal impairment	N (%)	499 (1.54%)	820 (0.69%)	4,906 (3.24%)	1,070 (1.33%)
	Rheumatoid arthritis	N (%)	437 (1.35%)	1,300 (1.09%)	398 (0.26%)	119 (0.15%)
	Stroke	N (%)	1,189 (3.68%)	3,134 (2.62%)	3,308 (2.18%)	537 (0.67%)
	Venous thromboembolism	N (%)	441 (1.37%)	1,172 (0.98%)	2,051 (1.35%)	599 (0.74%)
Previous use of ICA (0 to 365 days prior)	ICA broad	Median [Q25–Q75]	0.00 [0.00 – 0.00]	0.00 [0.00 –0.00]	0.00 [0.00– 0.00]	0.00 [0.00 – 0.00]
Time since diabetes diagnosis (days)	-	Median [Q25–Q75]	398 [16–- 2,398]	576 [50 – 1,369]	1,102 [265– 2,497]	430 [28– 1,354]

CPRD GOLD=Clinical Practice Research Datalink (CPRD) GOLD; DK-DHR=Danish Data Health Registries; FinOMOP-THL= Finnish Care Register for Health Care; SIDIAP=The Information System for Research on Primary Care

Patient characteristics of metformin users who underwent ICA procedures are described in **Table 6**. The median age [IQR] ranged from 62 [54, 71] years in DK-DHR to 71 [62,78] years in SIDIAP and these individuals were predominately male, ranging from 61% in CPRD GOLD to 73% in DK-DHR. The most common modality for ICA was X-ray (5% of cases in SIDIAP, 17% in CPRD GOLD, 72% in FinOMOP-THL, 87% in DK DHR) and CT scan (23% of cases in FinOMOP-THL, 27% in SIDIAP, 40% in CPRD GOLD). Overall, metformin users who underwent ICA procedures were older and had more comorbidities compared to the general metformin users. Of all these metformin users who underwent ICA procedures, 3% in CPRD GOLD, 42% in DK-DHR, 56% in FinOMOP-THL, and 50% in SIDIAP had hypertension. A higher proportion had a history of myocardial infarction and heart failure when compared with the general metformin user (from 6% CPRD GOLD to 24% in DK-DHR for myocardial infarction and from 1% in CPRD GOLD to 32% in DK-DHR for heart failure). The median duration of diabetes was longer in this cohort compared to the metformin users in SIDIAP and CPRD GOLD. Among metformin users who underwent an ICA procedure, median duration of diabetes ranged from 331 [72, 1818] days in DK-DHR to 2,430 [1,242, 3762] days in SIDIAP. The median days since metformin initiation ranged from 20 [10,13] days in FinOMOP-THL to 771 [286, 1568] days in SIDIAP.

Regarding renal health, the prevalence and stage of CKD in metformin users who underwent ICA procedures was inconclusive in DK-DHR and FinOMOP-THL with almost 100% missing data. Conversely, missing data was much lower in CPRD GOLD and SIDIAP, and we observed a high prevalence of CKD Stage 2 among metformin users who underwent ICA procedures in both: 51% and 37%, respectively. The prevalence of CKD stage 1 among this cohort was 10% in CPRD GOLD and 24% in SIDIAP. Metformin users who underwent ICA procedures had an estimated prevalence of CKD stage 3 at 20% in CPRD GOLD and 14% in SIDIAP. The prevalence of CKD stage 4 and 5 was estimated to be less than 1% in CPRD GOLD and SIDIAP.

Table 6. Baseline characteristics of individuals with an iodinated contrast agent procedure while taking metformin.

Variable name	Variable level	Estimate name	DK-DHR	FinOMOP-THL	SIDIAP	CPRD GOLD
Metformin + ICA cohort		N	529	526	9,795	231
Age	-	Median [Q25 – Q75]	62 [54 – 71]	66 [58–74]	71 [62–78]	69 [58 – 76]
Sex	Female	N (%)	145 (27.41%)	185 (35.17%)	3,477 (35.75%)	90 (38.96%)
CKD stage	Stage 1	N (%)	-	-	2,303 (23.51%)	24 (10.39%)
	Stage 2	N (%)	-	-	3,608 (36.84%)	117 (50.65%)
	Stage 3	N (%)	<5	-	1,418 (14.48%)	46 (19.91%)
	Stage 4	N (%)	-	-	49 (0.50%)	<5
	Stage 5	N (%)	-	-	13 (0.13%)	-
	Missing	N (%)	528 (99.81%)	526 (100.00%)	2,404 (24.54%)	42 (18.18%)
ICA type	CT scan	N (%)	-	119 (22.62%)	5,119 (52.26%)	91 (39.39%)
	X-ray	N (%)	458 (86.58%)	381 (72.43%)	819 (8.36%)	40 (17.32%)

Variable name	Variable level	Estimate name	DK-DHR	FinOMOP-THL	SIDIAP	CPRD GOLD
	Fluoroscopy	N (%)	61 (11.53%)	8 (1.52%)	3,089 (31.54%)	<5
	Other	N (%)	10 (1.89%)	-	468 (4.78%)	90 (38.96%)
	Missing	N (%)	-	<5	14 (0.14%)	-
	Duplicate	N (%)	-	14 (2.66%)	61 (0.63%)	8 (3.46%)
Comorbidities (0 to 365 days prior)	Anxiety	N (%)	24 (4.54%)	13 (2.47%)	757 (7.73%)	<5
	Asthma	N (%)	55 (10.40%)	45 (8.56%)	365 (3.75%)	9 (3.90%)
	Chronic kidney disease	N (%)	5 (0.95%)	<5	1,004 (10.25%)	<5
	Chronic liver disease	N (%)	9 (1.70%)	<5	252 (2.57%)	<5
	COPD	N (%)	51 (9.64%)	24 (4.56%)	1,302 (13.29%)	22 (9.52%)
	Dementia	N (%)	0 (0.00%)	8 (1.52%)	253 (2.58%)	0 (0.00%)
	GERD	N (%)	5 (0.95%)	<5	401 (4.09%)	<5
	Heart failure	N (%)	167 (31.57%)	103 (19.58%)	1,519 (15.51%)	10 (4.33%)
	HIV	N (%)	<5	<5	25 (0.26%)	0 (0.00%)
	Hypertension	N (%)	221 (41.78%)	295 (56.08%)	4,924 (50.27%)	6 (2.60%)
	Hypothyroidism	N (%)	15 (2.84%)	23 (4.37%)	649 (6.63%)	<5
	Inflammatory bowel disease	N (%)	<5	8 (1.52%)	49 (0.50%)	0 (0.00%)
	Malignant neoplastic disease	N (%)	38 (7.18%)	39 (7.41%)	1,432 (14.62%)	10 (4.33%)
	Myocardial infarction	N (%)	125 (23.63%)	122 (23.19%)	1,206 (12.31%)	13 (5.63%)
	Osteoporosis	N (%)	19 (3.59%)	<5	320 (3.27%)	<5
	Pneumonia	N (%)	72 (13.61%)	30 (5.70%)	865 (8.83%)	10 (4.33%)
	Renal impairment	N (%)	10 (1.89%)	5 (0.95%)	1,368 (13.97%)	6 (2.60%)
	Rheumatoid arthritis	N (%)	5 (0.95%)	8 (1.52%)	85 (0.87%)	<5

Variable name	Variable level	Estimate name	DK-DHR	FinOMOP-THL	SIDIAP	CPRD GOLD
	Stroke	N (%)	37 (6.99%)	60 (11.41%)	796 (8.13%)	<5
	Venous thromboembolism	N (%)	7 (1.32%)	9 (1.71%)	503 (5.14%)	12 (5.19%)
Time since diabetes diagnosis (days)	-	Median [Q25 – Q75]	331 [72 – 1,818]	323 [40 – 1,319]	2,430 [1,242 - 3,762]	1,190 [483 – 2,178]
Time since metformin start (days)	-	Median [Q25 – Q75]	69 [23 – 183]	20 [10 – 31]	771 [286–1,568]	405 [137 – 924]

CPRD GOLD=Clinical Practice Research Datalink (CPRD) GOLD; DK-DHR=Danish Data Health Registries; FinOMOP-THL= Finnish Care Register for Health Care; SIDIAP=The Information System for Research on Primary Care

9.2.2. Survival Analysis

9.2.2.1 Outcome Counts

Among metformin users who underwent an ICA procedure, the most frequently reported of the pre-specified events was AKI (CPRD GOLD: 7 events, DK-DHR: 5 events, FinOMOP-THL: 0 event, SIDIAP: 747 events). The cumulative incidence of AKI during the study period for metformin users with an ICA procedure in CPRD GOLD was 3%, 1% in DK-DHR, 0% in FinOMOP-THL, and 7.7% in SIDIAP. There were no events of ketoacidosis or lactic acidosis reported among metformin users with an ICA procedure in any of the databases, except in SIDIAP where 44 users had a record of ketoacidosis (**Table 7**).

Table 7. Number of events for the outcomes of acute kidney injury, ketoacidosis, and lactic acidosis among individuals with an iodinated contrast agent procedure while taking metformin.

Data Source	Number of events		
	AKI	Ketoacidosis	Lactic Acidosis
CPRD GOLD	7	0	0
DK-DHR	5	0	0
FinOMOP-THL	0	0	0
SIDIAP	747	44	0

CPRD GOLD=Clinical Practice Research Datalink (CPRD) GOLD; DK-DHR=Danish Data Health Registries; FinOMOP-THL= Finnish Care Register for Health Care; SIDIAP=The Information System for Research on Primary Care

9.2.2.1.1 Acute kidney injury survival probabilities

Probability of experiencing the outcome of AKI among metformin users from undergoing an ICA procedure to the end of follow up for each data source is as follows: CPRD 10% (95% CI: 0%, 20%), DK-DHR 2% (0%, 4%), SIDIAP 25% (22%, 29%). FinOMOP-THL had <5 events which precluded analysis. Kaplan-Meier curves are depicted in **Figure 4.**

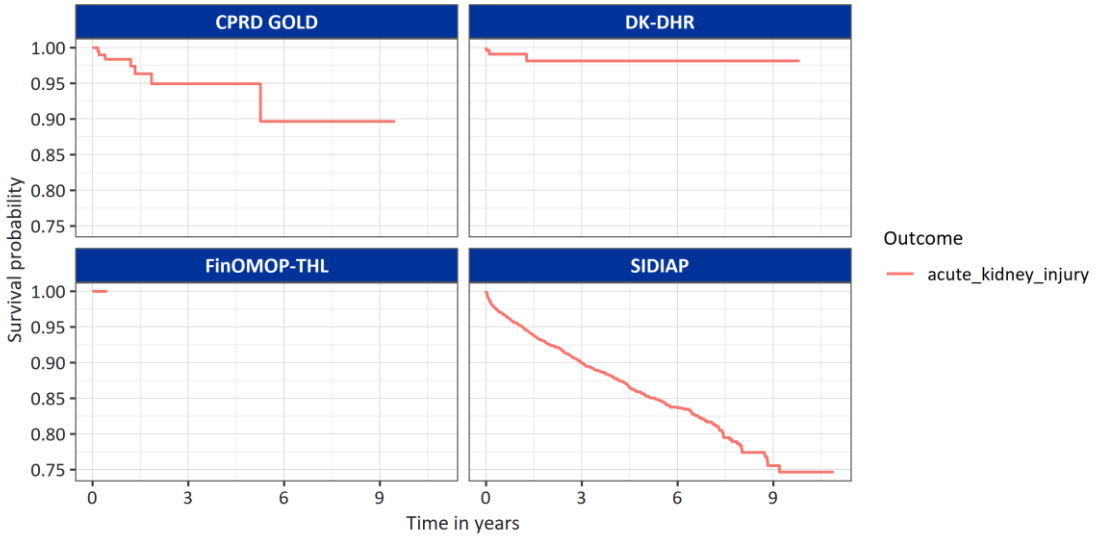

Figure 4. Kaplan-Meier curves for the outcome of acute kidney injury among individuals with an iodinated contrast agent procedure while taking metformin.

CPRD GOLD=Clinical Practice Research Datalink (CPRD) GOLD; DK-DHR=Danish Data Health Registries; FinOMOP-THL= Finnish Care Register for Health Care; SIDIAP=The Information System for Research on Primary Care

Figure 5 presents Kaplan-Meier curves for AKI stratified by CKD stage for each data source. In SIDIAP, when stratified by CKD stage, stage 1 had lowest probability of having a record of AKI at 9% (7%, 12%), and stage 4 had the highest probability 50% (1%, 71%).

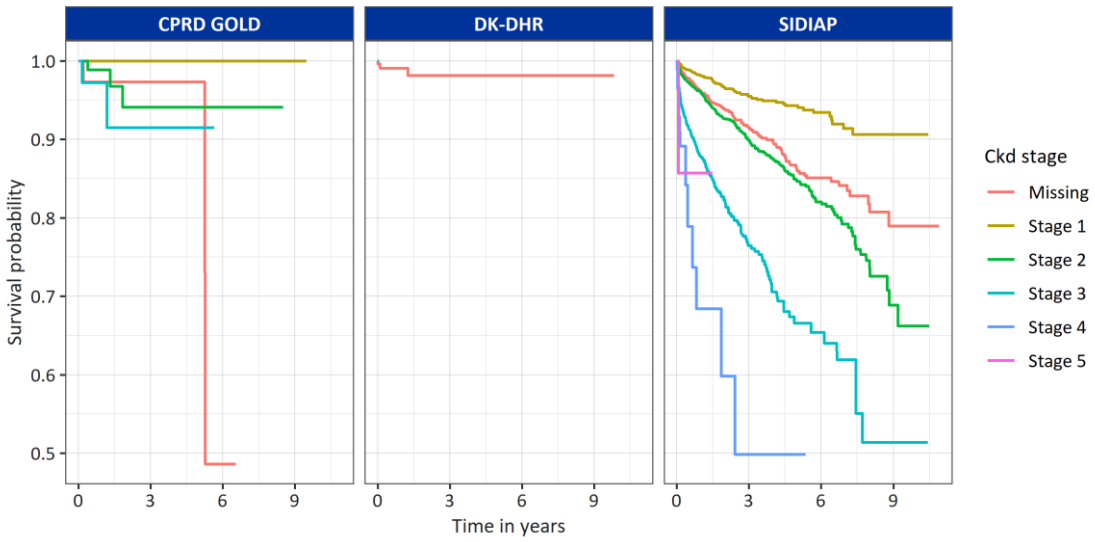

Figure 5. Kaplan-Meier curves for the outcome acute kidney injury among individuals with an iodinated contrast agent procedure while taking metformin, stratified by CKD Stage at the moment of ICA exposure.

CPRD GOLD=Clinical Practice Research Datalink (CPRD) GOLD; DK-DHR=Danish Data Health Registries; FinOMOP-THL= Finnish Care Register for Health Care; SIDIAP=The Information System for Research on Primary Care

As shown in **Figure 6**, there were no differences in occurrence of AKI when stratified by ICA type.

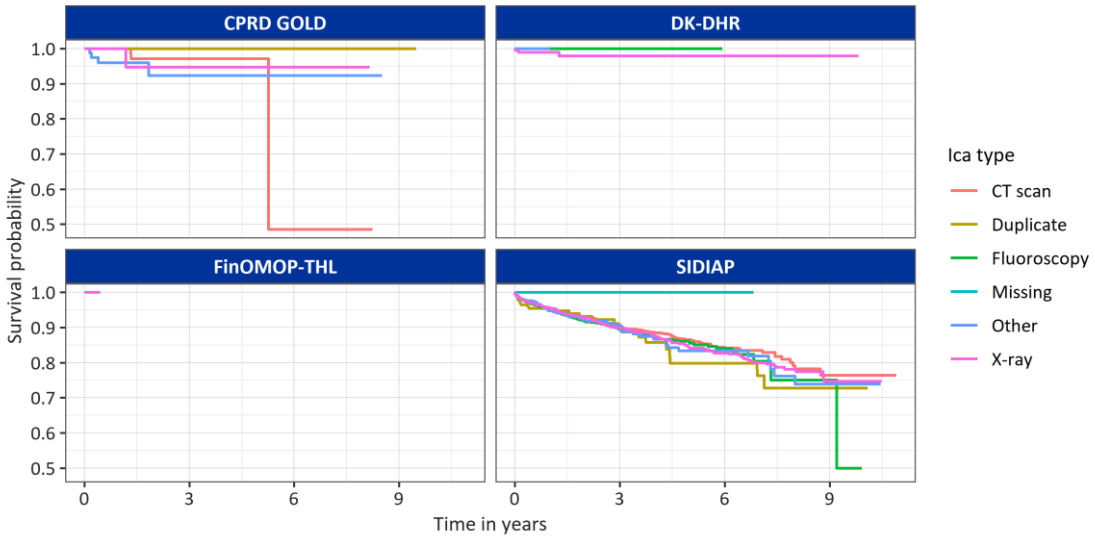

Figure 6. Kaplan-Meier curves for the outcome acute kidney injury among individuals with an iodinated contrast agent procedure while taking metformin, stratified by type of procedure.

CPRD GOLD=Clinical Practice Research Datalink (CPRD) GOLD; DK-DHR=Danish Data Health Registries; FinOMOP-THL= Finnish Care Register for Health Care; SIDIAP=The Information System for Research on Primary Care

9.2.2.1.2 Kaplan-Meier curves for ketoacidosis

There were no records of ketoacidosis in all data sources aside from SIDIAP. In SIDIAP, the probability of having a recording of ketoacidosis to the end of follow up was 2% (1%,3%). As shown in **Figures 7–9**, these results were consistent across CKD levels and ICA modalities.

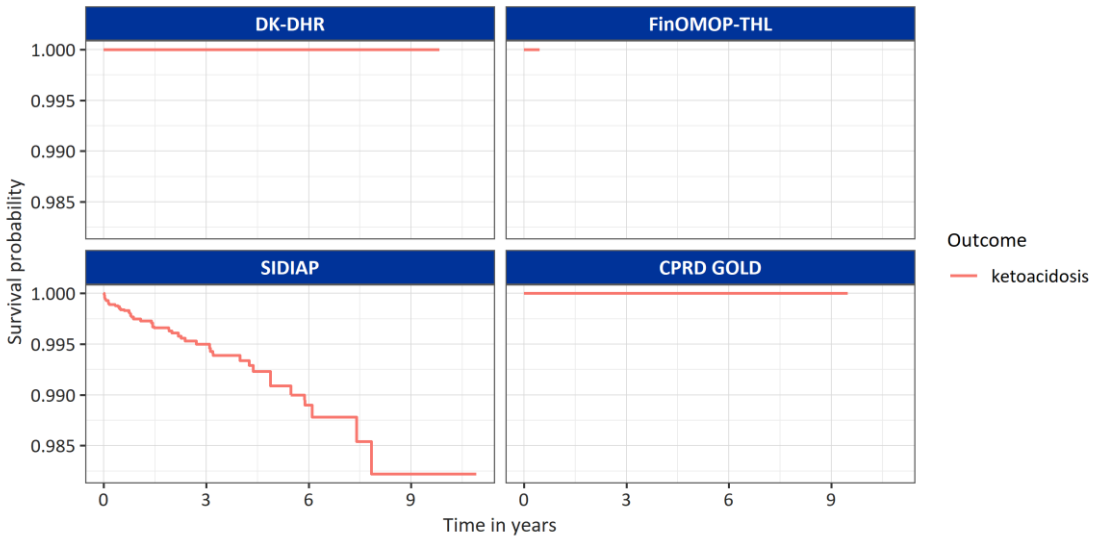

Figure 7. Kaplan-Meier curves for the outcome ketoacidosis among individuals with an iodinated contrast agent procedure while taking metformin.

CPRD GOLD=Clinical Practice Research Datalink (CPRD) GOLD; DK-DHR=Danish Data Health Registries; FinOMOP-THL= Finnish Care Register for Health Care; SIDIAP=The Information System for Research on Primary Care

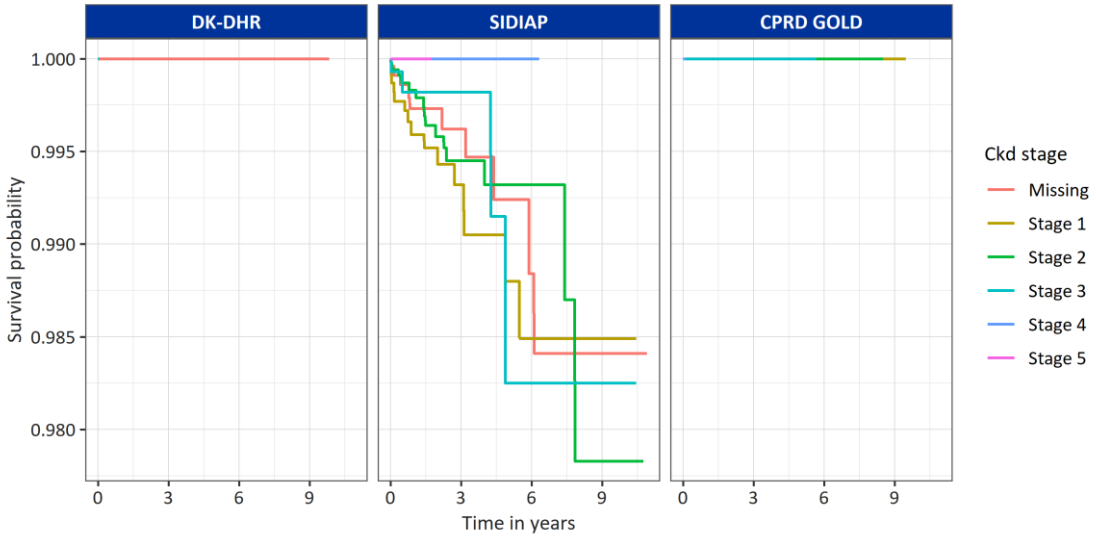

Figure 8. Kaplan-Meier curves for the outcome ketoacidosis among individuals with an iodinated contrast agent procedure while taking metformin, stratified by CKD Stage at the moment of ICA exposure.

CPRD GOLD=Clinical Practice Research Datalink (CPRD) GOLD; DK-DHR=Danish Data Health Registries; SIDIAP=The Information System for Research on Primary Care

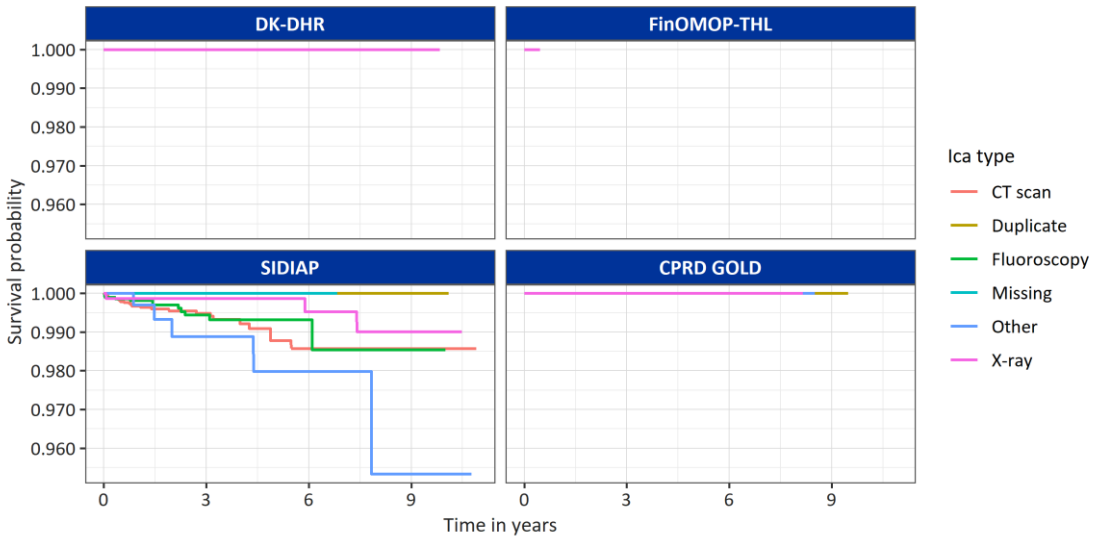

Figure 9. Kaplan-Meier curves for the outcome ketoacidosis among individuals with an iodinated contrast agent procedure while taking metformin, stratified by type of procedure.

CPRD GOLD=Clinical Practice Research Datalink (CPRD) GOLD; DK-DHR=Danish Data Health Registries; FinOMOP-THL= Finnish Care Register for Health Care; SIDIAP=The Information System for Research on Primary Car

9.2.2.1.3 Kaplan-Meier curves for lactic acidosis

There were <5 events for lactic acidosis across all data sources, which precluded analyses.

9.2.3. Changes in measurements

Among the data sources with measurement data, there were no changes in median eGFR from the last record prior to ICA procedure to the first record after ICA procedure. eGFR measurements are further described in **Table 8**.

Table 8. Change in eGFR measurements prior to and after ICA procedure among individuals with an iodinated contrast agent procedure while taking metformin.

Variable name	Estimate name	CDM name			
		DK-DHR	FinOMOP-THL	SIDIAP	CPRD GOLD
Number of metformin users who underwent ICA procedure	N	529	526	9,795	231
eGFR (prior year)	Median [Q25 –Q75]	–	–	81.00 [64.00 –90.00]	60.00 [59.00 –77.25]
	Range	–	–	[0.00– 90.00]	[24.00 –117.00]
eGFR (next year)	Median [Q25 –Q75]	–	–	81.00 [63.00 –90.00]	60.00 [59.00 – 72.50]
	Range	–	–	[0.00– 90.00]	[37.00 –108.00]
eGFR change	Median [Q25 –Q75]	–	–	0.00 [-4.00 –4.00]	0.00 [-3.00 –0.00]
	Range	–	–	[-88.00 – 72.00]	[-30.00 –35.00]

CPRD GOLD=Clinical Practice Research Datalink (CPRD) GOLD; DK-DHR=Danish Data Health Registries; FinOMOP-THL= Finnish Care Register for Health Care; SIDIAP=The Information System for Research on Primary Care

Figure 10 shows that among metformin users, CKD stage before and after ICA procedure were largely consistent for CPRD GOLD. A small proportion of metformin users changed to higher or lower CKD stages or missing after ICA procedure in SIDIAP. Due to the high degree of missing data for CKD stages in DK-DHR and FinOMOP-THL, plots were not produced.

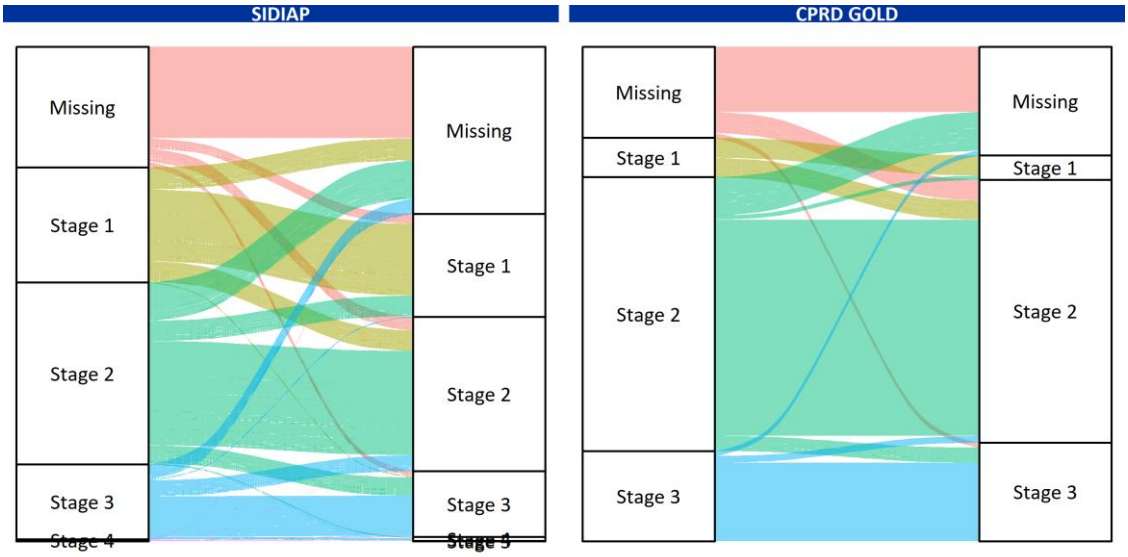

Figure 10. Changes in CKD Stage before and after undergoing a procedure requiring ICA among individuals with an iodinated contrast agent procedure while taking metformin.

CPRD GOLD=Clinical Practice Research Datalink (CPRD) GOLD; DK-DHR=Danish Data Health Registries; FinOMOP-THL= Finnish Care Register for Health Care; SIDIAP=The Information System for Research on Primary Care

9.3. Post-Hoc analyses: Results for DK-DHR cohorts with alternate metformin cohort

After analyses and review of the results, it was noted that while our metformin and ICA cohorts included individuals with a type 2 diabetes diagnosis prior to index date, DK-DHR had their indications recorded on index date. Thus, a number of individuals with their first prescription of metformin had their indication of type 2 diabetes recorded on the same day and was not captured in our original cohort definitions. In addition, DK-DHR eGFR measurements were mapped to a code which was not included in our original code list. Due to these insights, we conducted a post-hoc analyses in the DK-DHR data source to include individuals who had a diagnosis of type 2 diabetes on index date, and to include the new eGFR measurement code. We have presented the new records below and the new DK-DHR results in the shiny app are named as “DK-DHR-2”.

9.3.1. Patient Characterisation

Table 9 describes patient characteristics of the alternate metformin cohort The alternate metformin cohort consisted of a substantial increase in number of individuals from 32,302 individuals to 206,848. There was an increase in proportion of females from 42% in the original metformin cohort to 45% in the alternate metformin cohort. While our original cohort had 99.5% missing CKD staging, the alternate metformin cohort saw 48% of individuals with CKD stage 1 and 36% with CKD stage 2, with missing data consisting of only 7.2% of individuals in the alternate metformin cohort. Time since diabetes decreased from a median of 398 days in the original definition to 0 days in the alternate definition.

Table 9. Baseline characteristics of patients in DK-DHR with the alternate metformin cohort.

CDM name	Variable name	Variable level	Estimate name	Estimate value
DK-DHR-2	Number subjects	-	N	206,848
	Age	-	Median [Q25 – Q75]	60 [50 – 71]
	Sex	Female	N (%)	92,695 (44.81%)

CDM name	Variable name	Variable level	Estimate name	Estimate value
	CKD stage	Stage 1	N (%)	99,536 (48.12%)
		Stage 2	N (%)	75,097 (36.31%)
		Stage 3	N (%)	16,983 (8.21%)
		Stage 4	N (%)	328 (0.16%)
		Stage 5	N (%)	12 (0.01%)
		Missing	N (%)	14,892 (7.20%)
	Comorbidities (0 to 365 days prior)	Anxiety	N (%)	8,431 (4.08%)
		Asthma	N (%)	17,432 (8.43%)
		Chronic kidney disease	N (%)	824 (0.40%)
		Chronic liver disease	N (%)	979 (0.47%)
		COPD	N (%)	12,754 (6.17%)
		Dementia	N (%)	1,618 (0.78%)
		GERD	N (%)	608 (0.29%)
		Heart failure	N (%)	6,616 (3.20%)
		HIV	N (%)	275 (0.13%)
		Hypertension	N (%)	54,183 (26.19%)
		Hypothyroidism	N (%)	9,783 (4.73%)
		Inflammatory bowel disease	N (%)	1,545 (0.75%)
		Malignant neoplastic disease	N (%)	10,373 (5.01%)
		Myocardial infarction	N (%)	2,611 (1.26%)
		Osteoporosis	N (%)	5,739 (2.77%)
		Pneumonia	N (%)	14,512 (7.02%)
		Renal impairment	N (%)	1,038 (0.50%)
		Rheumatoid arthritis	N (%)	2,095 (1.01%)
		Stroke	N (%)	3,122 (1.51%)
		Venous thromboembolism	N (%)	1,766 (0.85%)
	Previous use of ICA (0 to 365 days prior)	ICA broad	Median [Q25 – Q75]	0.00 [0.00 – 0.00]
	Time since diabetes diagnosis (days)	-	Median [Q25 – Q75]	0 [0 – 0]

DK-DHR=Danish Data Health Registries

Table 10 describes patient characteristics of the alternate metformin cohort and individuals who underwent an ICA procedure. The number of individuals in the cohort increased from 529 using the original definition to 1,869 among individuals in the alternate metformin cohort who underwent an ICA procedure. There was a decrease in proportion of females from 27% in the original definition to 25% among individuals in the alternate metformin cohort who underwent an ICA procedure. While our original cohort had 99.9% missing CKD staging, among individuals in the alternate metformin cohort who underwent an ICA procedure saw 46% of individuals with CKD stage 1 and 39% with CKD stage 2, with missing data consisting of only 2.7% of individuals.

Table 10. Baseline characteristics of patients in DK-DHR among individuals in the alternate metformin cohort who underwent an ICA procedure.

CDM name	Variable name	Variable level	Estimate name	ICA
DK-DHR-2	Number subjects	-	N	1,869
	Age	-	Median [Q25 - Q75]	63 [55 - 71]
	Sex	Female	N (%)	466 (24.93%)
	CKD stage	Stage 1	N (%)	866 (46.33%)
		Stage 2	N (%)	723 (38.68%)
		Stage 3	N (%)	221 (11.82%)
		Stage 4	N (%)	6 (0.32%)
		Stage 5	N (%)	<5
		Missing	N (%)	51 (2.73%)
	ICA type	X-ray	N (%)	1,653 (88.44%)
		Fluoroscopy	N (%)	196 (10.49%)
		Other	N (%)	20 (1.07%)
	Comorbidities (0 to 365 days prior)	Anxiety	N (%)	63 (3.37%)
		Asthma	N (%)	173 (9.26%)
		Chronic kidney disease	N (%)	12 (0.64%)
		Chronic liver disease	N (%)	11 (0.59%)
		COPD	N (%)	159 (8.51%)
		Dementia	N (%)	<5
		GERD	N (%)	9 (0.48%)
		Heart failure	N (%)	413 (22.10%)
		HIV	N (%)	<5
		Hypertension	N (%)	785 (42.00%)
		Hypothyroidism	N (%)	72 (3.85%)
		Inflammatory bowel disease	N (%)	12 (0.64%)
		Malignant neoplastic disease	N (%)	95 (5.08%)

CDM name	Variable name	Variable level	Estimate name	ICA
		Myocardial infarction	N (%)	390 (20.87%)
		Osteoporosis	N (%)	46 (2.46%)
		Pneumonia	N (%)	219 (11.72%)
		Renal impairment	N (%)	18 (0.96%)
		Rheumatoid arthritis	N (%)	19 (1.02%)
		Stroke	N (%)	75 (4.01%)
		Venous thromboembolism	N (%)	26 (1.39%)
	Time since diabetes diagnosis (days)	-	Median [Q25 - Q75]	119 [33 - 433]
	Time since metformin start (days)	-	Median [Q25 - Q75]	83 [25 - 264]

DK-DHR=Danish Data Health Registries.

9.3.2. Survival Analysis

Among individuals in the alternate metformin cohort who underwent an ICA procedure, the outcome of AKI accumulated 11 events in DK-DHR. The cumulative incidence of AKI during the study period was 0.5%. There were no events recorded for the outcomes of ketoacidosis and lactic acidosis among the alternate ICA cohort.

Figures 11–13 illustrates the Kaplan-Meier survival curves for the outcome of AKI among the alternate ICA cohort, overall, stratified by CKD stage, and ICA type.

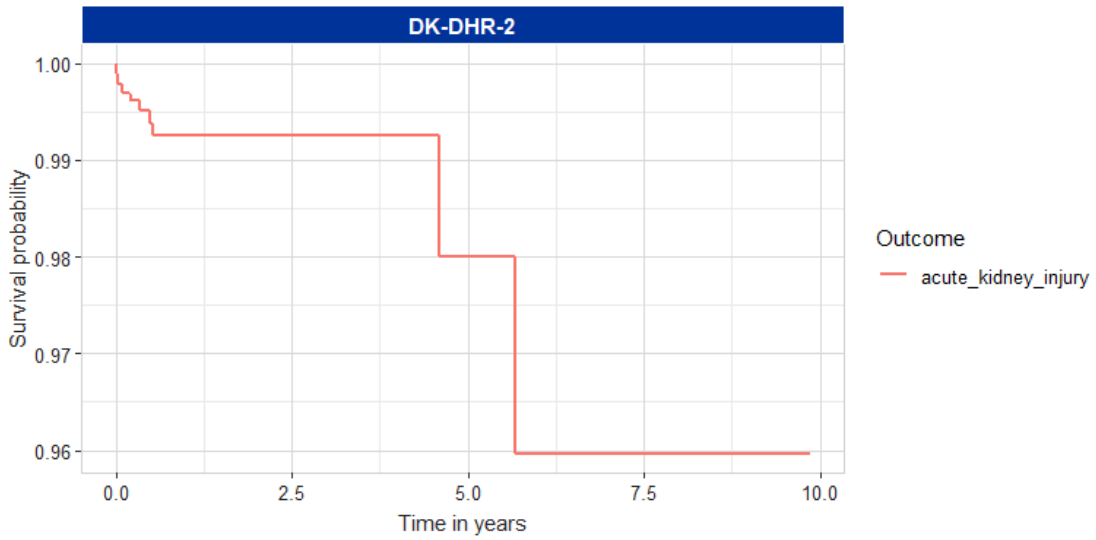

Figure 11. Kaplan-Meier curves for the outcome of acute kidney injury among individuals with an iodinated contrast agent procedure while taking metformin using the alternate metformin definition in DK-DHR.

DK-DHR=Danish Data Health Registries

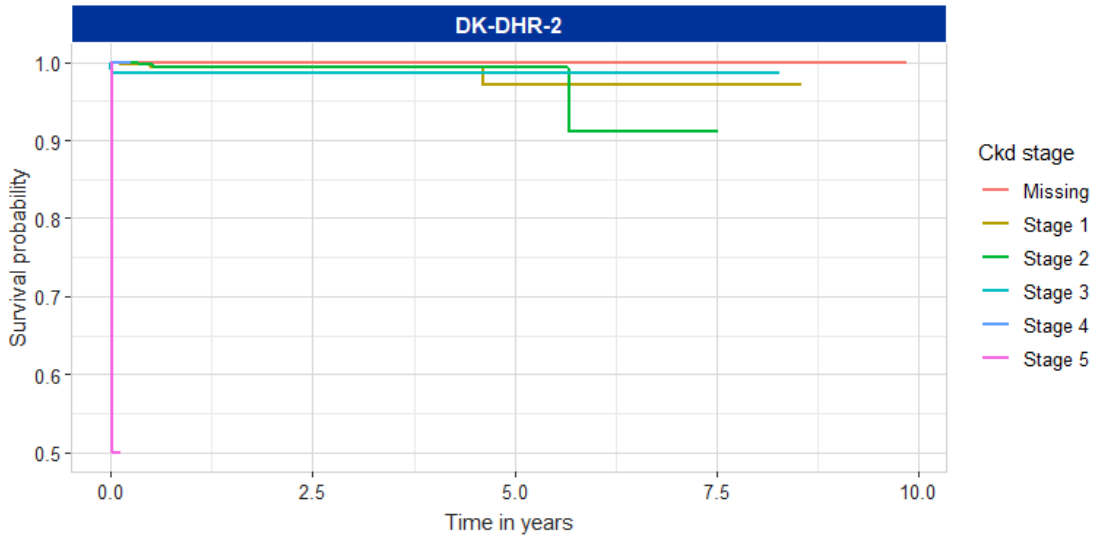

Figure 12. Kaplan-Meier curves for the outcome of acute kidney injury among individuals with an iodinated contrast agent procedure while taking metformin using the alternate cohort definition in DK-DHR, stratified by CKD stage.

DK-DHR=Danish Data Health Registries

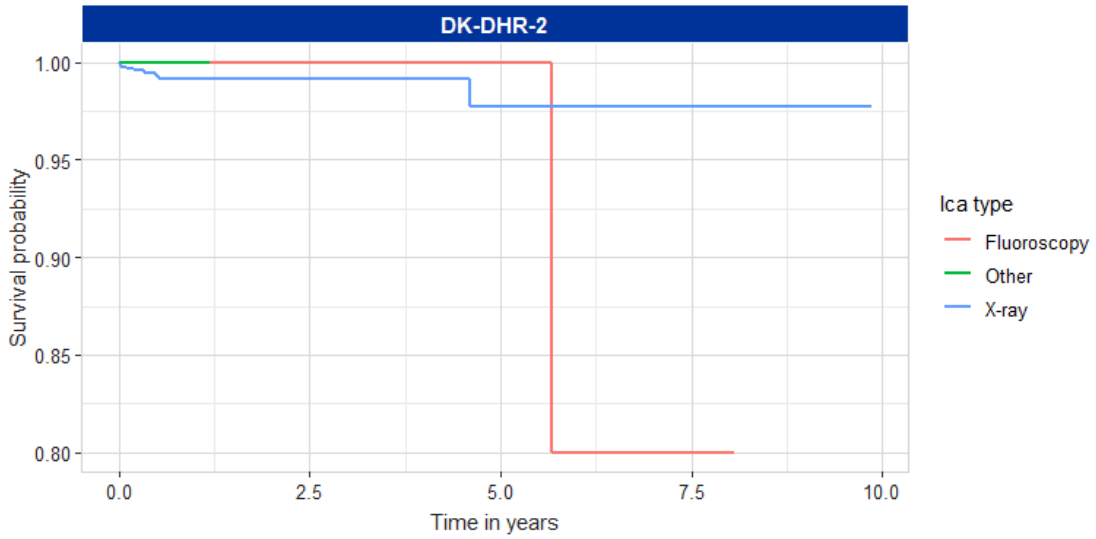

Figure 13. Kaplan-Meier curves for the outcome of acute kidney injury among individuals with an iodinated contrast agent procedure while taking metformin using the alternate cohort definition in DK-DHR, stratified by type of ICA.

DK-DHR=Danish Data Health Registries

9.3.3. Changes in measurements

While the original analysis did not have adequate data for changes in renal function, **Table 11** and **Figure 14** depict changes in eGFR measurements and CKD stage prior to and after ICA procedure with the new analyses. Median change in eGFR was 0 [IQR: -3.00 – 1.00]. There were some changes in CKD stages prior to and after ICA procedure, but staging was mostly consistent.

Table 11. Change in eGFR measurements prior to and after ICA procedure among individuals with an iodinated contrast agent procedure while taking metformin, with post-hoc analysis.

CDM name	Variable name	Variable level	Estimate name	Cohort name ICA
	Number of individuals	-	N	1,869
	eGFR (prior year)	-	Median [Q25 – Q75]	88.00 [70.25 – 90.00]
			Range	[4.00 –131.00]
	eGFR (next year)	-	Median [Q25 – Q75]	87.00 [70.00 – 90.00]
			Range	[4.00 –140.00]
	eGFR change	-	Median [Q25 - Q75]	0.00 [-3.00 – 1.00]
			Range	[-78.00 – 50.00]

DK-DHR=Danish Data Health Registries

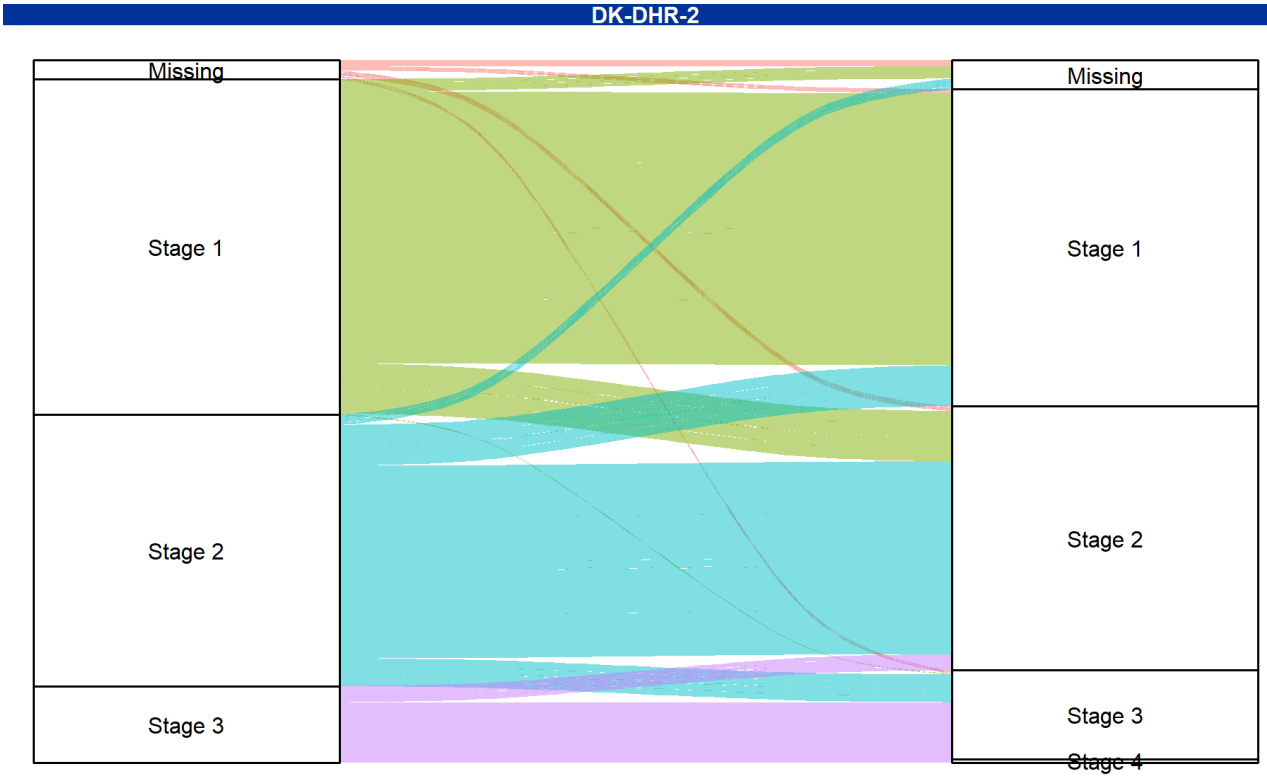

Figure 14. Changes in CKD Stage before and after undergoing a procedure requiring ICA among individuals with an iodinated contrast agent procedure while taking metformin.

DK-DHR=Danish Data Health Registries

10. DISCUSSION

10.1. Key results

This study characterised type 2 diabetes individuals taking metformin and type 2 diabetes individuals taking metformin who had a procedure requiring ICA in terms of acute renal outcomes across four European data sources, namely CPRD GOLD, DK-DHR, FinOMOP-THL, and SIDIAP. The cohort of patients treated with metformin ranged from 32,302 individuals in DK-DHR to 151,422 in SIDIAP, whereas the cohorts of metformin users who underwent an ICA procedure were substantially smaller with 231 individuals in CPRD GOLD, 529 in DK-DHR, 526 in FinOMOP-THL, and 9,795 in SIDIAP.

Patient characteristics were consistent across data sources. Metformin users were younger on average, with a median age ranging from 62 and 64, compared to metformin users who underwent an ICA procedure, with median age ranging from 62 to 71 year of age. Among metformin users who underwent an ICA procedure, individuals were predominately male, ranging from 61% in CPRD GOLD to 73% in DK-DHR. A higher proportion of individuals who underwent an ICA procedure had comorbidities, in particular hypertension (42% in DK-DHR, 56% in FinOMOP-THL, 50% in SIDIAP and 3% in CPRD GOLD), myocardial infarction (24% in DK-DHR, 23% in FinOMOP-THL, 12% in SIDIAP and 6% in CPRD GOLD), and heart failure (32% in DK-DHR, 20% in FinOMOP-THL, 16% in SIDIAP and 4% in CPRD GOLD). The most common modalities for ICA were X-ray and CT scan.

Among metformin users who underwent an ICA procedure, there were 747 AKI events and 44 ketoacidosis events in SIDIAP. The incidence of AKI events among metformin users followed from ICA procedure until the end of follow up was 3% in CPRD GOLD, 1% in DK-DHR, 0% in FinOMOP-THL, and 7.7% in SIDIAP. The cumulative incidence of AKI among metformin users who underwent an ICA procedure in SIDIAP differed across CKD stage, with stage 1 having the lowest incidence and stage 4 the highest incidence of AKI. The outcomes of ketoacidosis and lactic acidosis had very few events and Kaplan-Meier curves were not informative.

When evaluating changes in eGFR before and after ICA procedure, there were no changes seen for metformin users in CPRD GOLD or SIDIAP, whereas metformin users DK-DHR and FinOMOP-THL did not have measurements recorded. In addition, CKD stages were mostly consistent before and after ICA procedure for CPRD GOLD and SIDIAP and inconclusive for DK-DHR and FinOMOP-THL.

Post-hoc analyses in DK-DHR to include an alternate metformin definition where records of type 2 diabetes were captured on index date and inclusion for an additional eGFR measurement code, incurred more individuals in both the metformin users and the metformin+ICA users cohorts. However, among metformin users captured with the new definition and underwent an ICA procedure, AKI events were still low (11 events), no events of ketoacidosis or lactic acidosis, and there were no major trends in changes to CKD stage.

10.2. Strengths and limitations of the research methods

The study was informed by routinely collected health care data and thus data quality issues must be considered. A recording of a prescription or dispensation does not entail the patient taking the drug. In addition, assumptions around the duration of drug use exist.

Although some countries have guidelines regarding the discontinuation of metformin prior to procedures requiring ICA, given the nature of data sources using prescription and dispensation records, we were unable to assess whether patients discontinued their drug before ICA use.

The completeness of recordings of comorbidities used for patient characterization may vary across data sources. In addition, data completeness for measurement data may also vary across data sources. DK-DHR

and FinOMOP-THL did not have measurement data mapped. This limited the analysis of AKI and precluded any analysis of CKD stage before or after ICA exposure.

As there are no specific ingredient codes for ICA, we used procedure codes as a proxy. Two clinicians reviewed codes of imaging procedures where ICA is typically administered to generate our exposure definitions. The ICA procedure list was then reviewed by a specialist radiographer. Assumptions were made based on clinical guidelines of a certain region which may not generalize to other regions, and we cannot guarantee that ICA was administered during the procedure.

Data source specific limitations:

In DK-DHR, diagnosis of conditions in primary care are not consistently captured. Although incident type 2 diabetes diagnosis was not required for our study, there may have been some missed records of type 2 diabetes leading to fewer individuals included in the metformin cohort. To accommodate for potential missed recordings of type 2 diabetes, as DK-DHR incorporates indications in their prescription records on index date, we conducted a post-hoc analysis including patients with a type 2 diabetes record on index date for DK-DHR. This allowed us to capture more individuals in the Danish cohort, from 32,302 individuals to 206,848 in the metformin cohort and 529 individuals to 1,869 individuals among the ICA cohort. There were a low number of ICA procedures in DK-DHR due to poor mapping at the source level, as procedures were mapped to a broad level while our ICA definition was created using granular codes. This issue may have occurred in FinOMOP-THL as well. Additional mapping would not have fixed this, as source vocabularies for procedures is not granular enough to identify contrast use.

CPRD GOLD was not linked to hospital data, thus ICA procedures as well as the outcomes of AKI, ketoacidosis, and lactic acidosis, which are often recorded in a hospital setting, were not captured in our study.

10.3. Interpretation

There were low numbers of individuals in the ICA cohort for CPRD GOLD, DK-DHR, and FinOMOP-THL. As CPRD GOLD is a primary care data source, procedures in secondary care that require ICA, as well as outcomes of AKI, ketoacidosis, and lactic acidosis that are recorded in a hospital setting, were not well captured. In addition, the source vocabulary for procedures in DK-DHR was not granular enough to allow for the identification of ICA procedures (for example, CT scan of the cerebrum, CT scan of the kidneys, CT scan of the heart). In addition to having similar issues with lack of granularity of the source vocabulary, the mapping of procedures in FinOMOP-THL was incomplete.

The most AKI events were seen in SIDIAP, followed by CPRD GOLD. A potential explanation for these findings may be because these data sources included primary care data, which captured mild AKI events. DK-DHR and FinOMOP-THL only consisted of acute hospital-diagnosed AKI, likely missing some cases. SIDIAP consisted of hospital and primary care and had the longest follow up, which is reflected by the higher number of events captured by the data source. Previous studies with AKI as an outcome in CPRD GOLD and SIDIAP corroborate our cumulative incidence. In previous studies, among population of frail patients' cumulative incidence of AKI in CPRD GOLD linked with hospital episode statistics was 3% and another study found a cumulative incidence of 1.5% in the general population. [2,3] A study conducted in SIDIAP among those with CKD found a cumulative incidence of 7%. [4] In DK-DHR, our AKI events were low when compared to other studies as a benchmark. One study that captured AKI throughout the Danish Health System included plasma creatine (pCr) tests performed in primary care and at hospitals in Denmark and reported a cumulative incidence rate of 3% in the whole population during the follow up period. The codes for AKI in our study consisted of condition and diagnostic codes and did not include pCr measurements, likely missing some cases. [5] To our knowledge, there were no previous studies that reported AKI incidence among populations in FinOMOP-THL.

Differences in patient characteristics were observed between the metformin and ICA cohorts. In particular, individuals with ICA had more comorbidities, likely due to the potential indications for ICA. Intravascular contrast is administered in arteries for diagnostic catheter angiography and catheter-directed arterial intervention. Intravenous contrast administration is used for CT scans and to study the genitourinary tract and venous system. [6] The various indications for the use of ICA lends itself to a subset of the metformin cohort who are older and have more comorbidities. Many of the common comorbidities, such as hypertension, MI, and heart failure, may be reasons to obtain a procedure requiring ICA.

Current European Society of Urogenital Radiology guidelines from 2011 state that patients with an eGFR of 45 ml/min/1.73 m^2 or greater can continue to take metformin normally if they receive intravenous iodinated contrast medium. [7] However, the use of ICA poses risks, such as contrast induced AKI, with increased risk among those with renal dysfunction, diabetes, and poor cardiac function. [7] Our study found low numbers of events for AKI and high probabilities of remaining AKI-free during the follow up period for CPRD GOLD, DK-DHR, and FinOMOP-THL, which may be due to the small sample size in these cohorts. There were more events for SIDIAP and the probability of remaining AKI-free was higher at lower CKD stages. These findings are supported by previous studies conducted in hospital settings in Taiwan, where irrespective of diabetes diagnosis, an eGFR of less than 30 mL/min/1.73 m^2 was associated with higher odds of contrast induced AKI among patients with a contrast CT compared to a non-contrast CT.[8] Another study conducted in the emergency department in Taiwan found that contrast-enhanced CT was associated with higher risk of acute kidney injury and further haemodialysis among Taiwanese patients with an estimated glomerular filtration rate (eGFR) of less than 30 mL/min/1.73 m^2 but not those with an eGFR of more than 45 mL/min/1.73 m^2 .[9] Taken together, our findings and previous studies conducted in Taiwan suggest that the association of contrast on AKI is stronger among those with pre-existing renal dysfunction.

Historically, there were concerns over the increased risk for lactic acidosis among those taking metformin and undergoing a procedure requiring ICA. [10] However, studies have shown that the risk of metformin-induced lactic acidosis in diabetics is now recognised to be very low, with rates of 4.3 and 9 cases per 100,000 patient years reported. [11] Similarly, in our study, there were no events for lactic acidosis across the data sources.

10.4. Generalisability

The study comprised all individuals using metformin with prior diagnosis of type 2 diabetes in four data sources from four different European countries in primary care, registry, and secondary care settings. While we consider the results representative for the study population in the respective regions, the results should not be generalised to other countries or data sources but only reflect the situation in the specific region and setting covered by the respective data sources.

11. CONCLUSION

Our study shows that there were low numbers of individuals with an identifiable ICA procedure after metformin initiation in DK-DHR, FinOMOP-THL, and CPRD GOLD. The low frequency of ICA use among metformin users could potentially be due to lack of hospital records in CPRD GOLD and due to lack of granularity in source coding vocabularies in DK-DHR and FinOMOP-THL.

Overall, metformin users who underwent ICA procedures were older and had more comorbidities compared to the general metformin users. There were a low number of AKI events and no lactic acidosis and ketoacidosis events recorded in DK-DHR and FinOMOP-THL. However, patients in the metformin+ICA cohorts in CPRD GOLD and SIDIAP did have records of AKI and ketoacidosis. Cumulative incidence of AKI was therefore estimated at 3% in CPRD GOLD and 7.7% in SIDIAP.

Post-hoc analyses in DK-DHR to include a cohort definition for metformin users where type 2 diabetes was captured on index date and inclusion for an additional eGFR measurement code incurred more individuals

in both the metformin and ICA cohorts. However, AKI events were still low and there were no events of ketoacidosis or lactic acidosis recorded in the study cohort/s.

The regulatory motivation for this study was to assess whether existing real-world data in the DARWIN EU® network could be useful to evaluate compliance with the SmPC recommendation to temporarily interrupt metformin treatment around procedures involving ICA, and/or to compare safety outcomes according to whether this recommendation is followed. The limited numbers of patients eligible for our analyses in 3 of the 4 proposed data sources, together with the known lack of completeness and granularity on temporary and short-term drug discontinuation make it unlikely that further research using these data will be useful to answer the aforementioned regulatory objectives.

12. REFERENCES

1. EMA. Guideline on the clinical investigation of medicinal products to prevent development/slow progression of chronic renal insufficiency. 2016 Sep 15;(Committee for Medicinal Products for Human Use (CHMP)). Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-prevent-developmentslow-progression-chronic-renal-insufficiency_en.pdf
2. Oda T, Jödicke AM, Robinson DE, Delmestri A, Keogh RH, Prieto-Alhambra D. Oral Bisphosphonates Are Associated With Increased Risk of Severe Acute Kidney Injury in Elderly Patients With Complex Health Needs: A Self-Controlled Case Series in the United Kingdom. J Bone Miner Res. 2022 Jul 1;37(7):1270–8.
3. Sawhney S, Robinson HA, Veer SN van der, Hounkpatin HO, Scale TM, Chess JA, et al. Acute kidney injury in the UK: a replication cohort study of the variation across three regional populations. BMJ Open. 2018 Jun 1;8(6):e019435.
4. Robinson DE, Ali MS, Pallares N, Tebé C, Elhussein L, Abrahamsen B, et al. Safety of Oral Bisphosphonates in Moderate-to-Severe Chronic Kidney Disease: A Binational Cohort Analysis. J Bone Miner Res. 2021 May 1;36(5):820–32.
5. Jensen SK, Heide-Jørgensen U, Gammelager H, Birn H, Christiansen CF. Acute Kidney Injury Duration and 20-Year Risks of CKD and Cardiovascular Disease. Kidney Int Rep. 2024 Jan 22;9(4):817–29.
6. Pasternak JJ, Williamson EE. Clinical Pharmacology, Uses, and Adverse Reactions of Iodinated Contrast Agents: A Primer for the Non-radiologist. Mayo Clin Proc. 2012 Apr;87(4):390–402.
7. Stacul F, van der Molen AJ, Reimer P, Webb JAW, Thomsen HS, Morcos SK, et al. Contrast induced nephropathy: updated ESUR Contrast Media Safety Committee guidelines. Eur Radiol. 2011 Dec 1;21(12):2527–41.
8. Lee CC, Chan YL, Wong YC, Ng CJ, Chang CH, Hung CC, et al. Contrast-enhanced CT and Acute Kidney Injury: Risk Stratification by Diabetic Status and Kidney Function. Radiology. 2023 Jun;307(5):e222321.
9. Su TH, Hsieh CH, Chan YL, Wong YC, Kuo CF, Li CH, et al. Intravenous CT Contrast Media and Acute Kidney Injury: A Multicenter Emergency Department-based Study. Radiology. 2021 Dec;301(3):571–81.
10. Bettmann MA. Frequently Asked Questions: Iodinated Contrast Agents. RadioGraphics. 2004 Oct;24(suppl_1):S3–10.
11. Stang M, Wysowski DK, Butler-Jones D. Incidence of lactic acidosis in metformin users. Diabetes Care. 1999 Jun;22(6):925–7.

13. ANNEXES

ANNEX I. Description of data sources

Denmark: Danish Data Health Registries (DK-DHR)

#	Section	Description
1	Database Identification and country	DK-DHR (Danish Data Health Registries) Denmark
2	Data partner information section	Danish Medicines Agency (DKMA) Data Analytics Centre (DAC)
3	Coverage and timespan	Data collection since: 1995 Extent: Nation-wide. The data is representative of the entire Danish population.
4	Healthcare setting / type of data	Community pharmacists, and secondary care – specialists (ambulatory or hospital outpatient care), and hospital inpatient care. The following data elements are collected: diagnosis (including rare diseases and pregnancy data), hospital admissions, discharge and ICU data, Cause of death, Drug prescriptions, dispensing, vaccination and contraception, Procedures, Devices, and Sociodemographic information.
5	Data collection process	Outpatient electronic health records, and Inpatient hospital electronic health records, and Registries, and Other. All causes of deaths, all retrieved drug prescriptions, all records of vaccinations, all hospital inpatient and outpatients contacts including disease diagnoses and hospital surgical and non-surgical procedures, cancers, laboratory test results for the entire Danish population from 1/1/1995 onwards.
6	General representativeness	The data is representative of the entire Danish population. Healthcare is free in Denmark, so we do not expect any bias in data collection based on socio-economic status.
7	Data content /source coding	Diagnoses and causes of death are collected using the ICD-10 vocabulary. ATC and RxNorm are used for Drugs. SNOMED codes are used for Procedures.
8	Data Harmonization	The data has been mapped to the OMOP CDM v5.4 and the OMOP standard vocabularies (SNOMED, RxNorm, LOINC). The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. No.
9	Quality control (database specific)	The data we have received relating to nationwide Danish Health Data registries offer an opportunity for large-scale, population-based studies with several advantages 1) Their large size improves the precision of estimates and enables the study of rare exposures and outcomes with long-term latency, 2) Inclusion of nearly all individuals in the target population ensures that the data reflect routine clinical care and all clinical segments of the source population, 3) Data are collected independently of each research study, thus minimising certain types of bias, e.g., non-response, and the influence from attention to the research question on the diagnostic process. Before the source data is sent to us, the Danish Health Data Authority runs and does comprehensive checks of the registry table data validity of the variables, breaks in data, changes in variable coding, missingness, etc. We perform checks of missingness/completeness in relation to requested variables. In essence, we are receiving a dump of a mirror of the data that is controlled by the SDS. The documentation performed by SDS is available online, in Danish primarily https://www.esundhed.dk/Dokumentation (all variables), but also in English https://sundhedsdatastyrelsen.dk/da/english/health_data_and_registers/national_health_registers
10	Linkage	There is no linkage in this data source.
11	Vital status	The Cause of Death registry (DAR) is used, the cause of death is collected using ICD-10 codes.
12	Limitations	No database-specific limitations documented. General limitations for the data type applicable.

#	Section	Description
13	Main references	Schmidt M, Schmidt SAJ,Adelborg K,Sundbøll J,Laugesen K,Ehrenstein V,Sørensen HT "The Danish health care system and epidemiological research: from health care contacts to database records." Clinical epidemiology (2019): 31372058
14	Link to HMA-EMA catalogue and database webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/1111217 Website: https://sundhedsdatastyrelsen.dk/da/english/health_data_and_registers/healthdatadenmark

Finland: Finnish Care Register for Health Care (FinOMOP-THL)

#	Section	Description
1	Database Identification and country	FinOMOP-THL (Finnish Care Register for Health Care) Finland
2	Data partner information section	Finnish Institute for Health and Welfare (THL) Department of Knowledge Brokers
3	Coverage and timespan	Data collection since: 1998 Extent: Nation-wide. The current CDM population comprises all persons having been alive and residing in Finland since the beginning of 2011.
4	Healthcare setting / type of data	Primary care – gps, and primary care specialists (e.g., paediatricians), and secondary care – specialists (ambulatory or hospital outpatient care), and hospital inpatient care. The THL database covers both public and private, primary, and specialised inpatient and outpatient health care encounters in Finland, starting from 2011. The entire public sector and private inpatient encounters have been included since 2011, while private outpatient encounters, including occupational care, are included since 2020. Since 1998, the register has covered both public outpatient and inpatient specialized care and private inpatient care (TerveysHilmo). Since 2009, the Finnish National Vaccination Register is covered (complete since 2020). The vaccination register covers all vaccinations from the public sector and from a large part of private vaccination providers, with the data coverage from both sections being very good from 2020 onwards. Since 2011, the register has covered public primary care (AvoHilmo). Since 2020, the register has covered private outpatient care and occupational care. In addition, the CDM also contains positive COVID-19 test results from the Finnish National Infectious Diseases Register, which is maintained by THL.
5	Data collection process	Outpatient electronic health records, and Inpatient hospital electronic health records, and Registries. Data is entered by clinicians upon healthcare contact and processed by THL.
6	General representativeness	The THL data has national coverage and is therefore well representative of the Finnish population. Using the complete population as a basis for the person table also serves to facilitate calculations on a population level, e.g., incidence rates.
7	Data content /source coding	The following coding systems have been OMOP-mapped, typically to a good level of completeness: ICD10fi Finnish Extension, ATC, Toimenpideluokitus (procedure classification adapted from the Nordic Classification of Surgical Procedures (NCSP)), Terveydenhuollon erikoisalat (Hilmo specific provider speciality), Rokotustapa (AR/YDIN National classification for vaccine administration), Tupakointistatus (AR/YDIN National classification for smoking status). Vaccinations are identified on product level based on batch number, trade name, vaccine title, and ATC-code. This is mapped on brand and type in the OMOP CDM.
8	Data Harmonization	The data has been mapped to the OMOP CDM v5.4 and the OMOP standard vocabularies (SNOMED, RxNorm, LOINC). The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. Each patient in THL has a unique identifier.

#	Section	Description
9	Quality control (database specific)	The source data collection undergoes a structural and semantic validation before entry into the source database. Additionally, some coded variables undergo quality assessment against the respective code systems post entry into the database. The source registers are also assessed for completeness and coverage, with the aim of improving future collection in the areas where data is lacking.
10	Linkage	THL is already a linkage of multiple Finnish registries (see above).
11	Vital status	The National Population registry data forms the basis for forming the patient population. This ensures an up-to-date location (municipality of residence) of patients, as well as complete death occurrences (although not the cause of death).
12	Limitations	No database-specific limitations documented. General limitations for the data type applicable.
13	Main references	Häkkinen, Pirjo; Mölläri, Kaisa; Saukkonen, Sanna-Mari; Väyrynen, Riikka; Mielikäinen, Lasse; Järvelin, Jutta "Hilmo - Sosiaali- ja terveydenhuollon hoitoilmoitus 2020 : Määrittelyt ja ohjeistus : Voimassa 1.1.2020 alkaen" Terveyden ja hyvinvoinnin laitos (2019):
14	Link to HMA-EMA catalogue and database webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/1111187 Website: https://thl.fi/fi/tilastot-ja-data/ohjeet-tietojen-toimittamiseen/hoitoilmoitusjarjestelma-hilmo

Spain: The Information System for Research on Primary Care (SIDIAP)

#	Section	Description
1	Database Identification and country	SIDIAP (The Information System for the Development of Research in Primary Care) Catalunya, Spain
2	Data partner information section	IDIAPJGol
3	Coverage and timespan	Data collection since: 2006 Extent: Regional. The SIDIAP database contains records of around 6 million people residing in Catalonia, estimated to be representing around 76% of the Catalan population.
4	Healthcare setting / type of data	Primary care – gps, and hospital inpatient care. SIDIAP captured data includes routine visits, demographics, diagnoses, laboratory tests, drugs (prescribed and dispensed), referrals, and lifestyle information.
5	Data collection process	Outpatient electronic health records, and Inpatient hospital electronic health records, and Other. Data is entered by primary care physicians upon healthcare contact, supplemented with hospital discharge records. The Institut Catala de la Salut is the owner of the data and acts as the data controller.
6	General representativeness	It was previously shown that the captured SIDIAP population is highly representative of the entire Catalan region in terms of geographic, age, and sex distributions.
7	Data content /source coding	SIDIAP data covers all services that occur at the Primary Care Centres, as well as support services, such as sexual and reproductive health or home end-of-life care. Drugs are coded in ATC-WHO terminology in the source data. Health outcomes are captured in ICD-10CM codes. The SIDIAP contains all laboratory tests and results performed in primary health centres. Demographics, geographical, as well as socio-economic factors are recorded for each patient.
8	Data Harmonization	The data has been mapped to the OMOP CDM v5.4 and the OMOP standard vocabularies (SNOMED, RxNorm, LOINC). The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. No.
9	Quality control (database specific)	Internal and external validation processes are carried out to determine the data quality of the SIDIAP information at each data update.

#	Section	Description
		These include stratifying the data by geographical regions and year in order to identify differences in data collection that need to be harmonized (e.g., recording of specific information under different codes). The measurement units of variables measuring one characteristic are also homogenized (e.g., transformation of the data from every laboratory that measures haemoglobin to grams per decilitre). Visual inspection of all data included in the database by week is also conducted, allowing one to see temporal patterns in the registry of a certain variable. With this information, the SIDIAP team can issue recommendations to researchers about the most common variable(s) where certain information is recorded (e.g., there are several variables with information concerning the women's menopausal status and with these visual inspection tools the SIDIAP team can inform the researchers about which related variables have the largest number of records and could be more helpful to capture menopause). Data availability (longitudinally and reliability), plausibility (range checks and unusual values), and consistency are inspected through visualisation tools. In addition, before accessing the data for a requested project, research teams have access to a quality-control report. This document contains counts, years, percentiles, maximums and minimums, incidences, and prevalence of the data requested for the project, allowing detection of inconsistencies in the data extraction prior to data delivery. External validation processes of the SIDIAP database mainly include assessing the data recorded in SIDIAP through linkage to external gold standard data sources, by analysing free text, or by sending questionnaires to health professionals.
10	Linkage	SIDIAP is linked to a hospital discharge database, pharmacy dispensation, and primary care laboratories. It can also be linked to other registries in Catalonia on a project by project basis. . Additionally, SIDIAP data can be linked to hospital discharge data through the Data Analytics Program for Research and Innovation in Health (PADRIS, from its acronym in Catalan), which was requested and used for this study.
11	Vital status	Mortality is fully captured in SIDIAP. The cause of death is not available but can be linked to the Spanish death registry on a project by project basis.
12	Limitations	The SIDIAP data is not representative of individuals not using public primary care, and conditions that are usually followed by specialist care might not be properly captured. In addition, there is limited information on lifestyle variables. Patients are followed until Death or when transferring to another primary health care centre that does not contribute to SIDIAP.
13	Main references	Recalde M, Rodríguez C,Burn E,Far M,García D,Carrere-Molina J,Benítez M,Moleras A,Pistillo A,Bolíbar B,Aragón M,Duarte-Salles T "Data Resource Profile: The Information System for Research in Primary Care (SIDIAP)." International journal of epidemiology (2022): 35415748
14	Link to HMA-EMA catalogue and database webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/50190 Website: https://www.sidiap.org/index.php/en

The United Kingdom: Clinical Practice Research Datalink GOLD (CPRD GOLD)

#	Section	Description
1	Database Identification and country	CPRD GOLD (Clinical Practice Research Datalink GOLD) the United Kingdom
2	Data partner information section	University of Oxford NDORMS
3	Coverage and timespan	Data collection since: 1987 Extent: Nation-wide. CPRD GOLD consists of patients in contributing practices using Vision software. Historically this covered the whole of the UK, but the number of contributing practices in the England is dropping. In January 2025 only 3 practices from England were a part of CPRD GOLD, while historical patient data were from the whole of the UK, and will continue to be so. In the future,

#	Section	Description
		no practices from England will be present, only practices from Scotland, Wales, and Northern Ireland.
4	Healthcare setting / type of data	Primary care – gps, and primary care specialists (e.g., paediatricians), and secondary care – specialists (ambulatory or hospital outpatient care), and hospital inpatient care. CPRD GOLD data include patient demographics, biological measurements, clinical symptoms and diagnoses, referrals to specialist/hospital and their outcome, laboratory tests/results, and prescribed medications.
5	Data collection process	Outpatient electronic health records. Data is entered by clinicians into the EHR. Data is processed by CPRD and provides data releases for research.
6	General representativeness	CPRD GOLD has been assessed and found to be broadly representative of the UK general population in terms of age, gender, and ethnicity. In CPRD GOLD in January 2025 there were 2,730,707 current acceptable patients (i.e., registered at currently contributing practices that use Vision software, excluding transferred out, deceased patients, and those flagged by CPRD as not acceptable for clinical research for data quality issues). This equals to 4.07%, based on the UK population estimates of 67,026,300 from the Office of National Statistics (mid-2023). Current patients are only from Scotland, Wales, and Northern Ireland. Historically, GOLD does contain data from England as well.
7	Data content /source coding	Gemscript, Read, dm+d
8	Data Harmonization	The data has been mapped to the OMOP CDM v5.4 and the OMOP standard vocabularies (SNOMED, RxNorm, LOINC). The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. In GOLD, a patient can be registered under different ID numbers upon changing practice or re-registration. Researchers are not able to identify these patients, as the data are anonymised. However, GOLD covers less than 5% of the current UK GP practices and it is unlikely that an individual who does change GP practice ends up in another GP practice which uses the Vision software and accepts the CPRD data collection agreement. The very small number of duplicated IDs will have different observation periods and should not have an impact on the data analyses.
9	Quality control (database specific)	CPRD GOLD only includes practices whose data quality is assessed to be up-to-standard (uts). Each practice is associated to an uts date set when the data quality standards become satisfactory, and CPRD recommend using only longitudinal data starting from this uts date. Every time CPRD collect the EHR from a practice, checks are run for the data quality standards and if they are not adequate, the EHR is not accepted. When the data quality becomes acceptable again, CPRD updates the practice uts date. CPRD also check data quality standards at the patient level and associate each patient to a flag, reporting if its data is acceptable for clinical research. Only patients with acceptable data quality are included in the population to be mapped to CDM.
10	Linkage	CPRD GOLD can be linked to several sources, however our Oxford OMOP CDM is only linked to the CPRD GOLD Ethnicity Record and to the CPRD Townsend Deprivation Index at Practice Level
11	Vital status	Vital status is retrieved from the GP records. Population registry (ONS) data can be requested on a study-by-study basis and linked. This data only covers England and is planned to be mapped to OMOP in the future. The cause of death is not captured.
12	Limitations	The main limitation is due to the fact that CPRD GOLD is limited to GP records, and although it contains information on referrals and discharge letters, it may not fully capture specific hospital information. Events from hospital and specialist care are not covered.
13	Main references	Sanchez-Santos MT, Axson EL,Dedman D,Delmestri A "Data Resource Profile Update: CPRD GOLD." International journal of epidemiology (2025): 40499193
14	Link to HMA-EMA catalogue and database webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/1111113 Website: https://cprd.com

ANNEX III. Operational and reporting considerations

DATA MANAGEMENT

Data management

All data sources have previously mapped their data to the OMOP common data model. This enabled the use of standardised analytics and using DARWIN EU® tools across the network since the structure of the data and the terminology system was harmonised. The OMOP CDM was developed and maintained by the Observational Health Data Sciences and Informatics (OHDSI) initiative and is described in detail on the wiki page of the CDM: https://ohdsi.github.io/CommonDataModel and in The Book of OHDSI: http://book.ohdsi.org

The analytic code for this study was written in R and used standardized analytics wherever possible. Each data partner executed the study code against their data source containing individual data and then returned the results (csv files) which only contained aggregated data. The results from each of the contributing data sites were then combined in tables and figures for the study report.

Data storage and protection

For this study, personal data from individuals in various EU member states were processed, using information collected from national/regional electronic health record data sources. Due to the sensitive nature of this personal medical data, it is important to be fully aware of ethical and regulatory aspects and to strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy.

All data sources used in this study were already used for pharmaco-epidemiological research and have a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control were adhered to. In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses were run, which generate non-identifiable aggregate summary results.

QUALITY CONTROL

Data source quality control

When defining drug cohorts, non-systemic products will be excluded from the list of included codes summarised on the ingredient level.

When defining cohorts for indications, a systematic search of possible codes for inclusion will be identified using the *CodelistGenerator* R package (https://github.com/darwin-eu/CodelistGenerator). This package allows the user to define a search strategy and will use this to query the vocabulary tables of the OMOP common data model so as to find potentially relevant codes. In addition, the *CohortDiagnostics* (https://github.com/OHDSI/CohortDiagnostics) and *DrugExposureDiagnostics* (https://cran.r-project.org/web/packages/DrugExposureDiagnostics/index.html) R packages will be run, if needed, to assess the use of different codes across the data sources contributing to the study and identify any codes potentially omitted in error. The *DrugExposureDiagnostics* package evaluates ingredient-specific attributes and patterns in drug exposure records.

The study code will be based on DARWIN EU® R packages: *IncidencePrevalence* to estimate Incidence and Prevalence, *DrugUtilisation* to characterise the drug use, and *CohortCharacteristics* to characterise the cohort by indication. These packages will include numerous automated unit tests to ensure the validity of the codes, alongside software peer review and user testing. The R package will be made publicly available via GitHub.

ANNEX IV: List of stand-alone documents

Please see the supplemental document “ICA_codelist.csv”.

ANNEX V: Supplementary Tables

Table S1. Operational definition of time 0 (index date) and other primary time anchors.

Study population names	Time Anchor Description	Number of entries	Type of entry	Washout window	Care Setting[1]	Code Type	Diagnosis position	Incident with respect to…	Measurement characteristics/validation	Source of algorithm
All patients with incident use of metformin	Patient present in the database during the study period (2014–2024 [or latest date available]) and with at least 365 days of valid database history and a prior diagnosis of diabetes.	Single	Incident	[-Inf,1]	PC, SC	n/a	n/a	Metformin use	n/a	n/a
All patients with incident use of ICA during ongoing metformin use	Patient present in the database during the study period (2014–2024 [or latest date available]) and with at least 365 days of valid database history, a prior diagnosis of diabetes, and prior initiation of metformin	Single	Incident	[-inf,1]	PC, SC	n/a	n/a	ICA use after metformin initiation	n/a	n/a

[1] PC= primary care, SC= secondary care, n/a = not applicable

Table S2. Operational definitions of inclusion criteria.

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type	Diagnosis position	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Prior database history of 365 days	Study participants were required to have a year of prior history observed before contributing observation time in incidence calculations, and for characterisation of new users	After	[-365, -1]	PC, SC	N/A	N/A	All adults within selected data sources	N/A	N/A
Washout period/ new metformin use	New users were required to not have used metformin before	After	[-Inf, -1]	PC, SC	N/A	N/A	Population of new metformin users	N/A	N/A
Diagnosis of diabetes	Study participants were required to have a prior diagnosis of diabetes to be included in the study	After	[-Inf, -1]	PC, SC	N/A	N/A	Population of new metformin users, Population of metformin+ ICA users	N/A	N/A
Prior metformin use	New users were required to have initiated metformin during the study period, and metformin use on the index date.	After	[-inf,-1]	PC, SC	N/A	N/A	Population of metformin+ ICA users		

[1] PC= primary care, SC= secondary care, n/a = not applicable

Table S3. Operational definitions of exclusion criteria.

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type	Diagnosis position[2]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Outcome washout	Outcome of interest (AKI, lactic acidosis, diabetic ketoacidosis) prior to index date	After	[-365, 0]	PC, SC	N/A	N/A	Population of new metformin users, population of metformin+ ICA users	N/A	N/A
Metformin discontinuation	Metformin exposure ended prior to/at first procedure requiring ICA	After	[metformin initiation, 0]	PC, SC	N/A	N/A	Population of metformin+ ICA users	N/A	N/A

[1] PC= primary care, SC= secondary care, n/a = not applicable
[2] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

Table S4. Description of the selected data sources.

Country	Name of Data Source	Justification for Inclusion	Health Care setting	Type of Data	Number of active subjects	Feasibility count of exposure (Iodinated contrast agents)	Feasibility count of disease (acute kidney injury)	Data lock for the last update
Denmark	DK-DHR	Records to define population, intervention, comparator, and outcome of interest are documented in the patient records, as identified in the feasibility	Community pharmacists, secondary Care and Hospital in-patient care	EHR, Registry	6M	2,600 Person count (not mutually exclusive)	68,600 Person count	18/01/2025

Country	Name of Data Source	Justification for Inclusion	Health Care setting	Type of Data	Number of active subjects	Feasibility count of exposure (Iodinated contrast agents)	Feasibility count of disease (acute kidney injury)	Data lock for the last update
		request.						
Finland	FinOMOP-THL	Records to define population, intervention, comparator, and outcome of interest are documented in the patient records, as identified in the feasibility request.	Primary care, secondary care, hospital inpatient care	EHR, registries	5.7M	132,700 Person count (not mutually exclusive)	64,000 Person count	01/10/2024
Spain	SIDIAP	Records to define population, intervention, comparator, and outcome of interest are documented in the patient records, as identified in the feasibility request.	Primary care, hospital inpatient care	EHR	5.8M	112,600 Person count (not mutually exclusive)	269,400 Person count	10/10/2023
The United Kingdom	CPRD GOLD	Records to define population, intervention,	Primary care	EHR	17M	14, 000 Person count (not mutually exclusive)	74,900 Person count	17/08/2024

Country	Name of Data Source	Justification for Inclusion	Health Care setting	Type of Data	Number of active subjects	Feasibility count of exposure (Iodinated contrast agents)	Feasibility count of disease (acute kidney injury)	Data lock for the last update
		comparator, and outcome of interest are documented in the patient records, as identified in the feasibility request.						

CPRD GOLD=Clinical Practice Research Datalink (CPRD) GOLD; DK-DHR=Danish Data Health Registries; EHR = Electronic Health Records; FinOMOP-THL= Finnish Care Register for Health Care; SIDIAP=The Information System for Research on Primary Care

Table S5. Operational definitions of exposure.

Exposure group names	Details	Washout window	Assessment Window	Care Setting[1]	Code Type	Diagnosis position[2]	Applied to study populations	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm
Metformin use	Ingredient level: metformin ATC Code: A10BA02	[-inf,0]	At or after diagnosis of type 2 diabetes	PC, SC	RxNorm	N/A	Population of metformin new users and ICA new users	Previous metformin use	N/A	N/A
ICA use	Procedures that require an ICA are presented in a preliminary code list in a supplementary file.	(metformin use, 0]	After metformin initiation	PC, SC	Procedure codes	N/A	Metformin+ ICA users	Previous ICA use	N/A	N/A

[1] PC= primary care, SC= secondary care, n/a = not applicable
[2] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

Table S6. Operational definitions of outcome.

Outcome name	Details	Primary outcome?	Type of outcome	Washout window	Care Settings[1]	Code Type	Diagnosis Position[2]	Applied to study populations	Measurement characteristics/validation	Source of algorithm
AKI	Survival	Yes	Time to event	[-inf,0]	PC, SC	N/A	N/A	Metformin+ ICA users	N/A	N/A
Lactic acidosis	Survival		Time to event	[-inf,0]	PC, SC	N/A	N/A	Metformin+ ICA users	N/A	N/A
Diabetic ketoacidosis	Survival		Time to event	[-inf,0]	PC, SC	N/A	N/A	Metformin+ ICA users	N/A	N/A
Change in eGFR or CKD status before and after ICA initiation	Descriptive analyses: Proportion with a change of one or more CKD stage Median change in eGFR measurement		Categorical/ continuous	Was evaluated at the most recent record within 365 days prior to ICA initiation and the earliest record within 365 days after ICA initiation	PC, SC	N/A	N/A	Metformin+ ICA users	N/A	N/A

[1] PC= primary care, SC= secondary care, n/a = not applicable
[2] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

Table S7. Operational definitions of covariates.

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type	Diagnosis Position[2]	Applied to study populations	Measurement characteristics/ validation	Source for algorithm
Age	Age groups of <40, 40 –59, 60 –79, 80 and above years old	Categorical	At index date [0,0]	PC, SC	N/A	N/A	Metformin new users, Metformin+ ICA users	N/A	N/A
Sex	Male, female	Categorical	At index date [0,0]	PC, SC	N/A	N/A	Metformin new users, Metformin+ ICA users	N/A	N/A
Comorbidities	List of predefined conditions: - Anxiety, asthma, CKD, chronic liver disease, COPD, dementia, GERD, heart failure, HIV, hypertension, hypothyroidism, inflammatory bowel disease, malignant neoplastic disease, myocardial infarction, osteoporosis, pneumonia, rheumatoid arthritis, stroke, venous thromboembolism	Binary	[-365, 0]	PC, SC	SNOMED	N/A	Metformin new users, Metformin+ ICA users	N/A	N/A
Duration of diabetes	Time from diagnosis of diabetes to index date	Continuous (years/ months)	At index date [0,0]	PC, SC	N/A	N/A	Metformin new users, Metformin+ ICA users	N/A	N/A

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type	Diagnosis Position[2]	Applied to study populations	Measurement characteristics/ validation	Source for algorithm
Previous use of ICA	Yes/no	Binary	[-365, 0]	PC, SC	Procedure code	N/A	Metformin new users	N/A	N/A
CKD stage	Stages 1–5	Categorical	At index date [0,0]	PC, SC	N/A	N/A	Metformin new users, Metformin+ ICA users	N/A	N/A
ICA type	Fluoroscopy CT scans, X-ray Other	Categorical	At index date [0,0]	PC, SC	N/A	N/A	Metformin+ ICA users	N/A	N/A
Time from metformin initiation to first procedure requiring ICA	Time from metformin initiation to first procedure requiring ICA	Continuous (years/ months)	At index date [0,0]	PC, SC	N/A	N/A	Metformin+ ICA users	N/A	N/A

[1] PC= primary care, SC= secondary care, n/a = not applicable
[2] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter

ANNEX VI: Glossary

Additional definitions are available in the EMA Glossary of terms https://www.ema.europa.eu/en/about-us/glossaries.

Aggregated Data

Data collected and combined from multiple sources to generate summary information, typically anonymised.

Benefit-Risk Assessment

Evaluation of the positive therapeutic effects of a medicine compared to its risks (e.g., side effects).

Common Data Model (CDM)

A standardized data structure that enables data from multiple sources to be harmonized, making analysis consistent and reproducible. DARWIN EU® utilises the OMOP CDM maintained by the OHDSI community.

Complex Studies (C3)

Studies requiring the development or customisation of specific study designs, protocols, and Statistical Analysis Plans (SAPs), with extensive collection or extraction of data. Examples include etiological studies measuring the strength and determinants of an association between an exposure and the occurrence of a health outcome in a defined population considering sources of bias, potential confounding factors, and effect modifiers.

Coordination Centre (CC)

The central hub responsible for managing and overseeing the activities within DARWIN EU®. It is based at Erasmus University Medical Centre in Rotterdam, the Netherlands.

Data Access

The process of obtaining permission to use specific datasets for regulatory or scientific studies.

Data Quality Framework

A set of standards and procedures to ensure accuracy, completeness, timeliness, and consistency of data used in DARWIN EU®.

Data Source

A database or repository of structured health-related data, such as electronic health records (EHRs), insurance claims, or registries.

DARWIN EU®

The European Medicines Agency's (EMA) federated network of real-world data sources designed to generate evidence to support regulatory decision-making.

EMA (European Medicines Agency)

The regulatory body responsible for the evaluation and supervision of medicinal products in the EU, overseeing DARWIN EU®.

Evidence Generation

The process of analysing real-world data to produce scientific information that can inform healthcare or regulatory decisions.

Federated Network

A data infrastructure where data remain at their original location but can be analysed in a harmonised way across multiple partners using a common model and tools.

GDPR (General Data Protection Regulation)

The EU regulation governing the protection of personal data and privacy, crucial to how DARWIN EU® handles health data.

Health Technology Assessment (HTA)

A systematic evaluation of properties and impacts of health technology, often using DARWIN EU® data to support assessments.

Metadata

Descriptive information about a data source (e.g., its content, quality, and structure), essential for identifying relevant databases in DARWIN EU® studies.

Off-the-Shelf Studies (OTS)

Studies for which a standard protocol per study/analysis type and standardised analytics may be developed and applied or adapted, typically relating to a descriptive research question. This includes studies on disease epidemiology, for example, the estimation of the prevalence or incidence of health outcomes in defined time periods and population groups, or drug utilisation studies at the population or patient level.

OHDSI (Observational Health Data Sciences and Informatics)

An open-science collaborative community that develops tools and standards (including the OMOP CDM) to enable large-scale analytics of observational health data. OHDSI provides the technical and scientific foundation for DARWIN EU®'s analytical ecosystem.

Patient-Level Data

Data related to individuals, de-identified, used for longitudinal or detailed analyses.

OMOP (Observational Medical Outcomes Partnership)

A common data model (CDM) that standardises the structure and content of observational healthcare data, enabling systematic analysis across disparate datasets. DARWIN EU® uses the OMOP CDM to ensure interoperability and consistency in real-world evidence generation.

Real-World Data (RWD)

Data relating to individual health status or healthcare delivery that is collected from routine clinical practice rather than from randomised controlled trials.

Real-World Evidence (RWE)

Clinical evidence derived from the analysis of RWD, used to inform decisions by regulators, payers, or clinicians.

Regulatory Decision-Making

The process by which authorities like EMA assess data to authorise, monitor, or modify the use of medicines in the EU.

Routine Repeated Studies (RR)

Studies that are either Off-the-Shelf or Complex studies repeated on a regular basis, following the same protocol and study code, but with updated data and/or different data partners.

Study Protocol

A detailed plan describing how a specific real-world study will be conducted, including objectives, design, data sources, and analyses.

Very Complex Studies (C4)

Studies which cannot rely only on electronic health care databases, or which would require complex methodological work, for example, due to the occurrence of events that cannot be defined by existing diagnosis codes, including events that do not yet have a diagnosis code, where it may be necessary to combine a diagnosis code with other data such as results of laboratory investigations. These studies might require the collection of data prospectively, or the inclusion of new (not previously onboarded) data sources.