Risk of lactic acidosis associated with metformin use in patients with type 2 diabetes and moderate-severe chronic kidney disease: a case-control study (ALIMAR-C2)

First published: 05/07/2016

Last updated: 13/12/2018

Study Ongoing

Administrative details

PURI

https://redirect.ema.europa.eu/resource/26994

EU PAS number

EUPAS13969

Study ID

26994

DARWIN EU® study

No

Study countries

Spain

Study description

The use of metformin in patients with type 2 diabetes (2D) is rarely associated with lactic acidosis (LA) provided that contraindications do not exist. Though the safety information available in patients with moderate-severe chronic kidney disease (CKD) is limited and inconclusive, the use of metformin in this population is wide. This is a case-control study to assess the association between metformin and LA in patients with 2DM and moderate-severe CKD. It will be performed with computerized registered data from 16 Spanish hospitals and their areas of influence in primary care from 2010 to 2015, comprising more than 50 million person-years follow-up. Logistic regression will be used to assess the crude and adjusted risk of LA associated to metformin use overall and stratifying by use and dose categories and CKD stage. The overall case fatality rate of LA as well as the case fatality rate stratified by CKD stage will be calculated. Observation bias will also be explored.

Study status

Ongoing

Research institutions and networks

Institutions

Bellvitge University Hospital

First published: 01/02/2024

Last updated: 01/02/2024

Institution

IDIBELL

Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina, IDIAPJGol

Spain

First published: 05/10/2012

Last updated: 23/02/2024

Institution | Educational Institution | Laboratory/Research/Testing facility | Not-for-profit | ENCePP partner

Clinical Pharmacology Department, UASP Hospital Universitario Clinic Barcelona

Spain

First published: 29/03/2010

Last updated: 14/01/2025

Institution | Educational Institution | Hospital/Clinic/Other health care facility

University Hospital Vall d’Hebron (HUVH)

Spain

First published: 01/02/2024

Last updated: 01/02/2024

Institution | Educational Institution | Hospital/Clinic/Other health care facility

Institut de Recerca de l’Hospital de la Santa Creu i Sant Pau – IIB Sant Pau

First published: 01/02/2024

Last updated: 01/02/2024

Institution

Puerta de Hierro-Majadahonda University Hospital

First published: 01/02/2024

Last updated: 01/02/2024

Institution

Hospital La Paz

First published: 01/02/2024

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Institution

Hospital Clinico San Carlos

First published: 01/02/2024

Last updated: 01/02/2024

Institution

Hospital Universitario Virgen del Rocío

First published: 01/02/2024

Last updated: 01/02/2024

Institution

Hospital Vall d’Hebron,Hospital Germans Trias i Pujol,Hospital de La Santa Creu i Sant Pau. Barcelona, Spain. Fundación Jiménez Díaz,Hospital Universitario Puerta de Hierro,Hospital Ramón y Cajal,Servicio Madrileño de la Salud,Hospital La Paz,Hospital Clínico San Carlos Madrid, Spain. Hospital Universitario Virgen del Rocío Sevilla, Spain. Hospital Universitario Reina Sofía Córdoba,

Spain. Hospital Universitario Virgen de la Victoria y Regional de Málaga Málaga, Spain. Hospital Universitario de Cruces Barakaldo,Spain. Hospital Universitario Donostia San Sebastián, Spain. Hospital Universitario de Canarias Tenerife, Spain.

Contact details

Study institution contact

Consuelo Pedrós

Study contact

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Primary lead investigator

Consuelo Pedrós

Primary lead investigator

Study timelines

Date when funding contract was signed

Planned: 16/12/2015

Study start date

Planned: 01/02/2017

Actual: 01/02/2017

Data analysis start date
Planned: 01/12/2018

Date of final study report
Planned: 31/12/2019

Sources of funding

- Other

More details on funding

Institute of Health Carlos III, Subprogramme of Health Research Projects-Strategic Action in Health 2015 (file number PI15/00764)

Regulatory

Was the study required by a regulatory body?

No

Is the study required by a Risk Management Plan (RMP)?

Not applicable

Methodological aspects

Study type

Study type list

Study type:

Non-interventional study

Scope of the study:

Assessment of risk minimisation measure implementation or effectiveness

Main study objective:

To assess the association between use of metformin and lactic acidosis (LA) in patients with type 2 diabetes (2D) and moderate to severe chronic kidney disease (CKD).

Study Design

Non-interventional study design

Case-control

Study drug and medical condition

Anatomical Therapeutic Chemical (ATC) code

(A10BA02) metformin

metformin

(A10BD03) metformin and rosiglitazone

metformin and rosiglitazone

(A10BD05) metformin and pioglitazone

metformin and pioglitazone

(A10BD07) metformin and sitagliptin

metformin and sitagliptin

(A10BD08) metformin and vildagliptin

metformin and vildagliptin

(A10BD10) metformin and saxagliptin

metformin and saxagliptin

(A10BD11) metformin and linagliptin

metformin and linagliptin

Medical condition to be studied

Lactic acidosis

Chronic kidney disease

Type 2 diabetes mellitus

Population studied

Age groups

Adults (18 to < 46 years)

Adults (46 to < 65 years)

Adults (65 to < 75 years)

Adults (75 to < 85 years)

Adults (85 years and over)

Special population of interest

Renal impaired

Estimated number of subjects

147

Study design details

Outcomes

Occurrence of lactic acidosis. Case fatality rate.

Data analysis plan

Logistic regression will be used to estimate the crude and adjusted risk of LA associated to metformin overall and stratifying by dose and use categories and CKD stage. Covariables will include: age, sex, Charlson's comorbidity index, diabetic complications, liver disease, myocardial infarction, heart failure, acute renal failure, seizures, dehydration, gastroenteritis, shock, sepsis, respiratory failure, exposure to other antidiabetics, insulin, diuretics, RAS inhibitors, or NSAIDs, and others. The crude and adjusted risk of LA associated to other antidiabetics and insulin use will be also estimated. Sensitivity analyses will be performed to assess the homogeneity of data from different geographic regions and to exclude patients with missing covariables. The case fatality rate will be calculated as the proportion of patients dead during hospitalization. Observation bias will be analyzed by means of the frequency of lactate determination depending on the use of metformin.

Data management

ENCePP Seal

This study has been awarded the ENCePP seal

Conflicts of interest of investigators

Annex 5.Declaration of interests for ENCePP SEAL studies .pdf(467.52 KB)

Composition of steering group and observers

EUPAS13969-13968.pdf(7.63 KB)

Data sources

Data source(s)

The Information System for Research in Primary Care (SIDIAP)

Data sources (types)

Administrative healthcare records (e.g., claims)

Electronic healthcare records (EHR)

Other

Data sources (types), other

Computerized hospital information systems

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Unknown

Check completeness

Unknown

Check stability

Unknown

Check logical consistency

Unknown

Data characterisation

Data characterisation conducted

No