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





Administrative details

EU PAS number	
EUPAS13969	
Study ID	
26994	
DARWIN EIL® study	
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

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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: 23/05/2025 Institution Educational Institution Laboratory/Research/Testing facility Not-for-profit ENCEPP partner



University Hospital Vall d'Hebron (HUVH)

Spain

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Educational Institution

Hospital/Clinic/Other health care facility

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

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Institution

Puerta de Hierro-Majadahonda University Hospital

First published: 01/02/2024

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Institution

Hospital La Paz

First published: 01/02/2024

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Institution

Hospital Clinico San Carlos

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Hospital Universitario Virgen del Rocío

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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 cpedros@bellvitgehospital.cat

Study contact

cpedros@bellvitgehospital.cat

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

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

The use of the ENCePP Seal has been discontinued since February 2025.

The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

This study has been awarded the ENCePP seal

Conflicts of interest of investigators

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