

Current practices for communication and uptake of risk minimisation measures by healthcare professionals –

Example of risk of lactic acidosis after iodinated contrast media administration in patients taking metformin

Olivier Clément, MD, PhD

HCPWP plenary - 3 July 2024

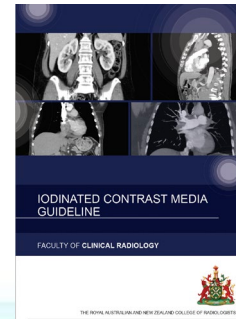
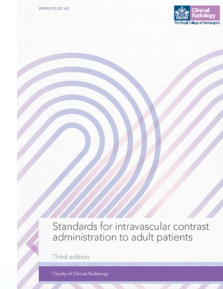
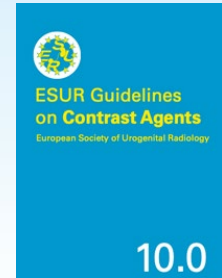
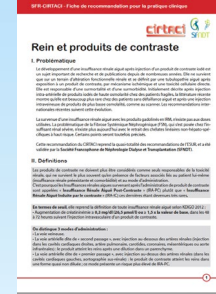
PROBLEM STATEMENT :

metformin and Iodinated Contrast Agents (ICA)

- Theoretical risk of lactic acidosis occurring related to transient acute kidney injury (AKI) induced by the contrast medium
- Decades ago, discontinuation of Metformin 2 days before until 2 days after ICA in all patients
- Later, discontinuation of Metformin at the time of injection and for the following 2 days in all patients
- 10 years ago, discontinuation only in patients with $\text{eGFR} < 60\text{ml/min}$
- In the last few years, discontinuation only in patients with $\text{eGFR} < 30\text{ml/min}$
- In parallel with the broadening use of metformin in diabetics

Learned Societies Guidelines

- ACR Manual on Contrast Media 2022
- ESUR CMSC Guideline V10 2018
- The Royal College of Radiologist 2015
- The Royal Australian and New Zealand College of Radiologists 2018
- French Cirtaci 2020
- Korean Clinical Practice Guidelines for Adverse Reactions to Intravenous Iodinate and MRI-Gadolinium Contrast Agents 2022



CONTRAST INDUCED NEPHROPATHY

Contrast-Associated Acute Kidney Injury

Risk Threshold

ACR	eGFR<30 , 30-45 not independent factor
ESUR	eGFR<30 IV, <45 IA first pass, Acute renal failure, IA, large dose
RCR UK	eGFR<40
AUS-NZ	eGFR<30
CIRTACI	eGFR <30

CONTRAST INDUCED NEPHROPATHY

Stop Metformin for 48 hrs

ACR

eGFR < 30 or AKI or Arterial

ESUR

eGFR < 30 or AKI or Arterial

RCR UK

eGFR <60 see clinician

AUS-NZ

eGFR < 30 or AKI or Arterial

CIRTACI

eGFR < 30 or AKI or Arterial

Pb: Guidelines not in accordance with SMPC of metformin

Administration of iodinated contrast media:

Intravascular administration of iodinated contrast agents may lead to contrast-induced nephropathy resulting in metformin accumulation and increased risk of lactate acidosis. **Metformin should be discontinued before or at the time of imaging procedure and should not be reinstated until at least 48 hours after**, provided that renal function has been evaluated and demonstrated to be stable.

Pb: Guidelines not in accordance with SMPC of metformin

ansm

Agence nationale de sécurité du médicament
et des produits de santé

Point d'information

« Acidose lactique et metformine : un risque évitable »

Nous alertons les professionnels de santé et les patients sur le risque d'acidose lactique avec la metformine, en particulier chez les patients avec une fonction rénale dégradée, une maladie cardio-respiratoire ou un sepsis (infection grave)

L'acidose lactique est un effet indésirable connu de la metformine. Elle peut conduire à une hospitalisation, voire au décès en cas de prise en charge trop tardive. Nous rappelons les situations susceptibles de favoriser son apparition et les signes qui doivent conduire à consulter en urgence un médecin.

La metformine est indiquée dans le traitement du diabète de type 2. Elle est éliminée par le rein et s'accumule dans le sang lorsque la fonction rénale est dégradée, ce qui favorise l'acidose lactique. Ce risque d'effet indésirable grave peut être limité par les mesures suivantes :

Pb: Guidelines not in accordance with SMPC of metformin

- difficultés à respirer,
- diminution de la température corporelle et du rythme cardiaque.
- **Le traitement par metformine doit être temporairement interrompu :**
 - Au moment de l'administration de produits de contraste iodé selon les préconisations du Résumé des Caractéristiques du Produit.
 - **En cas de déshydratation** (diarrhée, vomissements, fièvre ou diminution de l'apport en liquides), **la metformine doit être temporairement arrêtée** et il est recommandé de contacter un professionnel de la santé.

Metformin must be stopped before or at the time of imaging and can be restored after a 48hrs delay....

Recent Meta-analyses

European Radiology (2023) 33:6290–6298
<https://doi.org/10.1007/s00330-023-09611-2>

European Radiology
ESRF EUROPEAN SOCIETY
OF RADIOLOGY

CARDIAC



Appraisal of guidelines for managing contrast medium in patients with metformin: consensuses, controversies, and gaps

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European Radiology (2022) 32:3045–3055
<https://doi.org/10.1007/s00330-021-08395-7>

CONTRAST MEDIA



Continuous use of metformin in patients receiving contrast medium: what is the evidence? A systematic review and meta-analysis

Ting-Wan Kao¹ · Kuo-Hua Lee^{2,3,4} · Wing P. Chan^{5,6} · Kang-Chih Fan^{7,8} · Che-Wei Liu^{9,10} · Yu-Chen Huang^{10,11,12} 

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Cardiology

CAD and AMI: Systematic Review

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Metformin Can Be Safely Used in Patients Exposed to Contrast Media: A Systematic Review and Meta-Analysis

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Recent Meta-analyses

- Risk of lactic acidosis is low
- Threshold (30 ml/min/m² discussed)

Risk Minimisation Measures

- Problem to overstate the risk of metformin
 - examination postponed
 - diagnosis not made
 - risk/benefit balance
- Radiologists and Cardiologists lost: who to believe ?
- Need for clarification

Dr Sabine Straus

Chair, PRAC

European Medicines Agency

Domenico Scarlattilaan 6

1083 HS Amsterdam

The Netherlands

Vienna, July 12, 2023

Ref.: **Metformin suspension for Radiological procedures.**

Dear Dr Straus,

The discontinuation of Metformin therapy for diabetic patients at the time of injection of an iodine based contrast medium has been a constant issue for Radiologists over the last several decades.

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De: AskEMA No-Reply AskEMA.noreply@ema.europa.eu
Objet: AskEMA - Response to ASK-147431 - Metformin and contrast media
Date: 4 août 2023 à 15:35
À: olivier.clement@aphp.fr



Dear Mr Clement,

Thank you for your letter to the PRAC chair regarding a discrepancy between recent radiology guidelines and the current recommendation in the summaries of product characteristics (SmPCs) for metformin-containing medicines concerning concomitant use of iodinated contrast injection. This has been handed to me for responding.

We can confirm that in 2016, as an outcome of an EU-wide review led by EMA's human medicines committee (CHMP), EMA recommended updating the product information of metformin-containing medicines to remove the contraindication for use in patients with moderately reduced kidney function for the treatment of type 2 diabetes.

Follow-Up

- Glucophage being the originator medicine
- Mutual recognition procedure. The reference Member State for Glucophage is France
- Need to discuss the issue with the marketing authorisation holder
- Contact with the MAH: no new scientific evidence to change the warning

What is next ?

- This story shows the difficulty to update and harmonise SmPC with evolving science data
- Different interests between doctors/patients and the MAH
 - MAH maximise the warnings and contra indications
 - Patients/doctor : optimise the risk/benefit balance
- What shall we do to go on ?