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Discontinuation of metformin in the setting of coronary angiography: clinical uncertainty amongst physicians reflecting a poor evidence base

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KEYWORDS

- metformin
- lactic acidosis
- coronary angiography
- guidelines

Abstract

Aims: Metformin is widely prescribed for the treatment of type 2 diabetes mellitus and is associated with a reduction in diabetes-induced cardiovascular morbidity and mortality. Concerns about metformin-associated lactic acidosis (M-ALA) in patients undergoing contrast-based angiographic procedures have led to the development and publication of a number of guidelines to improve the management of this patient cohort.

Methods and results: This review focuses on the evidence behind these guidelines and, in particular, that concerning metformin discontinuation in diabetic patients undergoing coronary angiography and percutaneous intervention. This review addresses and compares guideline-directed management of such patients and includes the results of a UK physician survey to highlight variations in clinical practice.

Conclusions: We conclude that evidence for M-ALA in diabetics on metformin undergoing coronary intervention is lacking and existing guidance on the management of such patients is inconsistent. More robust evidence is needed in the form of a large, adequately-sized randomised trial or extensive registry so that we can optimally manage those patients requiring contrast-based coronary interventions who are also taking metformin.

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Introduction

Metformin, a biguanide, was introduced in 1957 for the treatment of non-insulin dependent diabetes mellitus[1]. Metformin may also be used in combination with insulin and is the most widely prescribed oral agent in diabetes[2]. It exerts its effects primarily by decreasing hepatic gluconeogenesis and glycogenolysis[3], and by increasing skeletal muscle glucose uptake[4]. Metformin is also associated with a reduction in cardiovascular morbidity and mortality, when compared to insulin or sulfonylureas[5]. The plasma half-life of metformin is between four and 8.7 hours in patients with normal renal function[6], with 90% being eliminated via renal excretion within 24 hours[7]. The biguanide agent that preceded metformin, phenformin, was withdrawn from clinical practice in 1978, since it was associated with an unacceptable risk of lactic acidosis[8], ranging from 40 to 64 cases per 100,000 patient-years[9]. Phenformin had been shown to impair oxidative phosphorylation in the liver, thereby increasing lactate production through anaerobic pathways[10]. Metformin has an estimated risk of lactic acidosis ten to twenty times less than that of phenformin[11], as a result of different pharmacokinetics[12].

Metformin use in the setting of coronary angiography and percutaneous coronary intervention

Concerns about metformin-associated lactic acidosis (M-ALA) have led to the practice of metformin discontinuation prior to diagnostic angiography and percutaneous coronary intervention (PCI), since lactic acidosis is a serious condition, with an estimated mortality rate of approximately 50%[13]. The incidence of M-ALA has recently come into question, such that the case could be made that routine discontinuation of metformin could carry the converse risk of it not being recommenced, which may lead to deleterious effects on glycaemic control and increased cardiovascular risk[14].

Evidence for metformin-associated lactic acidosis

The evidence that metformin use is associated with lactic acidosis **(Table 1)** has evolved from case reports on metformin treatment[15,16]. The mechanism for M-ALA has been associated with decreased gluconeogenesis from lactate, which could in theory cause lactate accumulation under circumstances such as acute renal failure[17]. Metformin itself is not directly nephrotoxic[18]. In patients predisposed to acute deterioration in renal function after contrast administration, i.e., contrast-induced nephropathy (CIN), it has been postulated that there is the potential for metformin to accumulate, leading to lactic acidosis. However, evidence for this is poor. Firstly, although CIN occurs in 2% to 25% of patients undergoing coronary intervention[19], not every patient on metformin that develops CIN develops M-ALA[18]. Secondly, most of the reported cases of lactic acidosis in patients taking metformin have been in patients with severe underlying conditions, including renal dysfunction, septicaemia, hepatic failure and acute left ventricular failure, any of which could in themselves contribute to the lactic acidosis[20-23]. Among the first million patients (approximately) to have received metformin in the United States, the Food and Drug Administration received 47 confirmed reports of lactic acidosis, and of these only four patients had no other apparent risk factors for lactic acidosis: 13 had pre-existing renal insufficiency; 30 had pre-existing cardiac disease, of whom 18 had congestive cardiac failure; three had chronic pulmonary disease and hypoxia; and eight were older than

Table 1. Summary of evidence.

Study and year	Type of study	Results
Salpeter et al[16] 2010	Meta-analysis of 347 prospective comparative trials and observational cohort studies.	No cases of fatal or non-fatal lactic acidosis were found in 70,490 patient-years of metformin use, nor in 55,451 patient-years in the non-metformin group.
Cryer et al[25] 2005	Multicentre randomised controlled trial, which compared outcomes at one year in diabetics taking metformin (n=7,227) to "usual care" (n=1,505).	No cases of lactic acidosis were reported in either group.
Stades et al[20] 2004	Systematic review of published case reports of M-ALA, from 1959 to 1999.	Of the 47 cases of M-ALA included, only one case had no other risk factors for lactic acidosis. 44 had at least one acute risk factor for lactic acidosis, including acute renal failure, sepsis and acute cardiac disease. The remainder had chronic risk factors. In 26% of the 47 cases contrast medium was administered.
McCartney et al[21] 1999	Systematic review of published and unpublished case reports of M-ALA after intravenous contrast administration.	Seventeen of the 18 cases of M-ALA reported had renal dysfunction, or the presence of other contraindications, before the administration of contrast.
Nawaz et al[22] 1998	Retrospective case series of 33 in-patients receiving metformin who underwent angiography.	Four of the patients with abnormal renal function prior to angiography died. 2 of the deaths were attributed to acute lactic acidosis and renal failure.
Misbin et al[23] 1998	Summary of reports of lactic acidosis, received by the Food and Drug Administration, in the United States, from 1995 to 1996.	Of the 47 confirmed reports of lactic acidosis, only 4 patients had no other apparent risk factors for lactic acidosis.

M-ALA: metformin-associated lactic acidosis

eighty[23]. Furthermore, lactic acidosis has been reported in diabetics not taking metformin, typically secondary to underlying conditions in which there was significant tissue hypoxia, such as acute left ventricular failure[24]. No specific study has addressed the impact of chronic metformin therapy versus recently started metformin on M-ALA.

Evidence for the safety of metformin has been reported in a large randomised controlled trial (the Comparative Outcomes Study of Metformin Intervention Versus Conventional Approach [COSMIC] study), which compared outcomes at one year in diabetics taking metformin (n=7,227), to "usual care", i.e., diabetics treated with a sulfonylurea, thiazolidinedione, insulin, or any other non-metformin monotherapy or combination therapy (n=1,505)[25]. No cases of lactic acidosis were reported in either group.

A recent meta-analysis, by Salpeter et al[16] on M-ALA, using pooled data from 347 prospective comparative trials and observational cohort studies, found no cases of fatal or non-fatal lactic acidosis in 70,490 patient-years of metformin use nor in 55,451 patient-years in the non-metformin group. Using Poisson statistics with 95% confidence interval the authors reported that the upper limit for the incidence of M-ALA was 4.3 cases per 100,000 patient-years, and in the non-metformin group the upper limit for the incidence of lactic acidosis was 5.4 cases per 100,000 patient-years. The mean blood lactate level measured during metformin treatment (1.24±0.31 mmol/l), was not significantly different from that in patients on non-metformin therapies (weighted mean difference 0.04 mmol/l, 95% confidence interval 0.00 to 0.13, p=0.07)[16]. Additionally, the net change from baseline lactate levels (1.13±0.25 mmol/l), was no different in patients on metformin compared to non-metformin therapies. The authors concluded that there was no evidence that metformin was linked to an increased risk of lactic acidosis, or with increased lactate levels, compared to other anti-hyperglycaemic treatments[16]. However, most patients in these studies received metformin in the absence of routinely recommended contraindications such as renal failure. Furthermore, the meta-analysis[16] did not address the issue of M-ALA in patients receiving contrast agents or in the setting of coronary angiography. The risk of M-ALA in patients undergoing coronary interventions is yet to be determined, with no published trial or registry data, but it is likely to be influenced by baseline renal function and volume of contrast agent used[26].

Guidelines

Despite the findings of a previous randomised controlled trial[25] and meta-analysis[16], concerns regarding M-ALA have led to the development of strategies designed to reduce the potential incidence of M-ALA in patients on metformin undergoing coronary angiography and/or PCI. Existing guidelines on the management of such patients have been published by several professional organisations **(Table 2)**[27-33].

According to guidelines from the National Institute for Health and Clinical Excellence in the UK[33], metformin should be withdrawn if serum creatinine is ≥150 µmol/l, or the estimated glomerular filtration rate (eGFR) is <30 ml/minute/1.73^2. Recommendations on the timing of discontinuing metformin prior to contrast administration vary depending on which guidelines are studied, and range from discontinuation 48 hours prior to the procedure[30,32], 24 hours prior to the procedure[28], or on the day of the procedure[29]. According to the American College of Cardiology (ACC)/American Heart Association (AHA)/Society for Cardiovascular Angiography and Interventions (SCAI) statement[28], metformin need only be withheld for 24 hours prior to performing PCI, "especially" in those with pre-existing renal dysfunction. By way of contrast the 2005 Royal College of Radiology (RCR) guidelines[30] in the UK indicate that if serum creatinine is raised and contrast injection is deemed necessary, metformin should be withheld for 48 hours prior to contrast administration. These guidelines[30] do not specify the level of creatinine at which renal function is deemed "abnormal", however, the 2009 RCR updated guidelines[31] advise that if serum creatinine is above the normal reference range, or eGFR <60 ml/minute/1.73[31], any decision to stop metformin for 48 hours should be made in "consultation with the referring physician". The European Society of Cardiology (ESC) Guidelines on myocardial revascularisation[27] recommend that in patients with renal impairment, metformin should be stopped before the procedure and suggest that an acceptable alternative to withholding metformin in all patients might be to check renal function after angiography and to stop metformin if renal function deteriorates. However, even these guidelines lack a robust evidence base, and have classed the recommendation of stopping metformin 48 hours prior to PCI in patients with known renal impairment as level of evidence C.

If metformin is discontinued, the ACC/AHA/SCAI[28] and RCR[30] guidelines advise restarting it 48 hours post contrast administration. However, existing guidelines are inconsistent in their recommendations on whether there is a need to recheck renal function prior to recommencing metformin[15], and if so when is the best time, or whether this should be conducted according to dye load. The ACC/AHA/SCAI[28] guidelines do not specify whether or not renal function should be reassessed prior to recommencing metformin, whereas the RCR[30] guidelines advise that if baseline renal function is impaired, renal function should be reassessed prior to recommencing metformin.

Current practice in the UK: results of a physician survey

We have collected information from UK physicians on their understanding of the management of patients on metformin booked to undergo coronary interventions, to better understand any variation in everyday clinical practice, and to determine to what degree local practice/strategies concur with published guidelines. In our study, an electronic questionnaire **(Table 3)** was sent to 1,240 cardiovascular physicians from a central database throughout the UK, in November 2009. The questionnaire set out to determine views on the role of guidelines in the management of patients booked for contrast exposure on chronic metformin therapy and to determine, if any, the variation in practice. It included sections on: (i) presence and use of local guidelines, (ii) understanding of discontinuation

Table 2. Summary of published guidelines on the use of metformin in patients requiring intravenous or intra-arterial contrast administration.

Source of guideline	Advice
ESC (2010)[27]	It is generally stated that metformin should be interrupted before angiography or PCI, and reintroduced 48 hours later, only after assessment of renal function. However, there is no convincing evidence for such a recommendation. Checking renal function after angiography in patients on metformin and stopping metformin when renal function deteriorates might be an acceptable alternative to suspension of metformin in all patients. In patients with renal failure, metformin should preferably be stopped before the procedure.
ACC/AHA/SCAI (2005)[28]	Whenever possible, metformin (especially in those with pre-existing renal dysfunction) should be withheld for 24 hours prior to performing PCI and for 48 hours afterwards.
RANZCR (2009)[29]	In patients with normal renal function, metformin does not need to be stopped providing that a moderate amount of contrast is used (≤100 ml). There is no need to retest the renal function.
	In patients with renal impairment, metformin should be withheld for at least 48 hours commencing on the day of the contrast study. Renal function should be reassessed before recommencing metformin.
RCR (2005)[30]	If serum creatinine is normal, and a low volume of contrast agent (≤100 ml) is to be administered, no special precaution is required.
	If serum creatinine is normal, but >100 ml of contrast or the intra-arterial route is used, metformin should be withheld for 48 hours after the procedure.
	If serum creatinine is raised, the need for contrast agent should be re-assessed. If contrast injection is deemed necessary, metformin should be withheld for 48 hours before and 48 hours after the contrast is given and the renal function re-assessed before restarting metformin treatment.
RCR Update (2009)[31]	If serum creatinine is normal, and/or eGFR >60 ml/minute/1.73^2, there is no need to stop metformin.
	If serum creatinine is above the normal reference range, or eGFR <60 ml/minute/1.73^2, any decision to stop metformin for 48 hours should be made in consultation with the referring physician.
ESUR (2008)[32]	For elective procedures:
	If eGFR is >60 ml/min/1.72 m^2 (or serum creatinine is normal) continue metformin.
	If eGFR is between 30 and 60 ml/min/1.72 m^2 (or serum creatinine is raised) discontinue metformin 48 hours prior to administration of contrast medium. Measure renal function at 48 hours after contrast medium administration and only restart metformin if renal function has not deteriorated.
	If eGFR is <30 ml/min/1.7 2m^2 metformin is not approved in most countries and iodinated contrast medium should be avoided if possible.
NICE (2009)[33]	Metformin should be withdrawn if serum creatinine is ≥150 µmol/l, or the eGFR <30 ml/minute/1.73^2.

ESC: European Society of Cardiology; ACC: American College of Cardiology; AHA: American Heart Association; SCAI: Society for Cardiovascular Angiography and Interventions; PCI: percutaneous coronary intervention; RANZCR: Royal Australian and New Zealand College of Radiologists; RCR: Royal College of Radiologists; eGFR: estimated glomerular filtration rate; ESUR: European Society of Urogenital Radiology; NICE: National Institute for Health and Clinical Excellence

criteria including definitions of renal impairment, (iii) the timing of metformin cessation, and its recommencement, (iv) renal function testing, and (v) views on the value of current guidelines. A total of 121 fully completed questionnaires were returned, representing a 10% response rate. Responses were received from centres throughout the UK, including: London; Oxford; Cambridge; East Midlands: North and South; West Midlands; Kent; Surrey and Sussex; Leeds; Sheffield; Newcastle; Manchester; Liverpool; Severn; the South West Peninsula; Scotland; Ireland; and Wales. Therefore, this spread of regional responses from an unbiased physician approach may indeed provide a snapshot of the variance in what is currently being practised in the UK.

Local guidelines were in place in 89% of units. In those following local guidelines, the majority of respondents (51.9%) did not know which professional body guidelines the local recommendations were based on. In those following guidelines published by professional bodies, approximately 50% reported that they followed the RCR guidelines and 50% reported that they followed the ACC/AHA/SCAI guidelines.

Of all respondents, 94% routinely check renal function prior to elective coronary intervention. However, there is widespread uncertainty as to the definition of impaired renal function, with 36% of respondents using estimated glomerular filtration rate (eGFR) alone, 28% using creatinine alone and only 20% using eGFR, creatinine and urea, to define renal impairment.

Eighty-eight percent of physicians routinely discontinue metformin prior to coronary angiography, irrespective of baseline renal status. Twenty-eight percent felt that discontinuing metformin did not make a significant difference to outcome. Of those who discontinue metformin, there was no consistency in the discontinuation period with 9% discontinuing over 48 hours prior to procedure, 45% 48 hours prior to procedure, 17% 24 hours prior to procedure, and 28% on the day of procedure **(Table 4)**. Of the total respondents in our study, 94% do not routinely check renal status post-procedure unless there is an abnormal pre-procedural result, for instance in a pre-admission clinic measurement. Recommencement timing ranged from 24 hours (17%) to more than 48 hours (19%) post-procedure. The overriding message borne out from this survey

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Table 3. Questionnaire.

Managing patients on metformin due to undergo angiography: an audit questionnaire.

PART A

1. Do you have specific local guidelines for the management of patients on metformin undergoing coronary angiography?
   - ☐ Yes
   - ☐ No
2. If yes, are these based on:
   - ☐ National guidelines from the Royal College of Radiologists
   - ☐ International guidelines from the European Society of Urogenital Radiology
   - ☐ International guidelines from the ACC or AHA
   - ☐ Guidelines from the Royal Australian and New Zealand College of Radiologists
   - ☐ Don't know
   - ☐ None of the above
3. If there are no local guidelines do you follow any of these Guidelines yourself:
   - ☐ National guidelines from the Royal College of Radiologists
   - ☐ International guidelines from the European Society of Urogenital Radiology
   - ☐ International guidelines from the ACC or AHA
   - ☐ Guidelines from the Royal Australian and New Zealand College of Radiologists
   - ☐ Other

   If other please specify which _____

PART B

1. Do you routinely test for renal function prior to elective coronary angiography?
   - ☐ Yes
   - ☐ No
2. Do you, or your team, specifically and routinely check the results of renal function tests in all cases prior to coronary angiography?
   - ☐ Yes
   - ☐ No
3. a) Do you routinely test renal function after coronary angiography in all cases?
   - ☐ Yes
   - ☐ No

   b) If not, in which circumstances would you test for renal function after coronary angiography?
   - ☐ Patients with prior abnormal renal function tests
   - ☐ Other

   If other please specify _____

   c) When (in hours) would you test renal function after coronary angiography?
4. How do you define abnormal renal function?

   eGFR (ml/min/1.72 m^2) <

   Creatinine (µmol/L) >

   Urea (mmol/L) >
5. Do you use a nomogram to determine eGFR?
   - ☐ Yes
   - ☐ No
   - ☐ Don't know
6. Do you routinely discontinue metformin in all patients who undergo coronary angiography?
   - ☐ Yes
   - ☐ No
7. a) If your answer to question 6 was no, do you routinely discontinue metformin in patients with abnormal renal function who undergo angiography?
   - ☐ Yes
   - ☐ No
   - ☐ Don't know

   b) If yes, at what level of abnormal eGFR would you stop the metformin?
   - ☐ Any figure below the normal range for eGFR
   - ☐ Mild renal dysfunction (i.e. eGFR 60 -89 ml/min/1.72 m^2)
   - ☐ Moderate renal dysfunction (i.e. eGFR 30 -59 ml/min/1.72 m^2)
   - ☐ Severe renal dysfunction (i.e. eGFR ≤29 ml/min/1.72 m^2)

   If other please specify _____

   c) If yes, at what level of abnormal creatinine would you stop the metformin?
   - ☐ Any figure above the normal range for serum creatinine (> 120 µmol/L)
   - ☐ Serum creatinine ≥130 µmol/L
   - ☐ Serum creatinine ≥150 µmol/L

   If other please specify _____

8. If you discontinue metformin, which of the following procedures would you stop metformin for?
☐ Coronary Angiography
☐ Cath? PCI
☐ PCI

9. If you discontinue metformin when would you stop it?
☐ >48 hours before the procedure
☐ 48 hours before the procedure
☐ 24 hours before the procedure
☐ On the day of the procedure
☐ Do not know
If other please specify _____

10. If you discontinue metformin when would you restart it?
☐ 24 hours after the procedure if renal function has not deteriorated
☐ 48 hours after the procedure if renal function has not deteriorated
☐ >48 hours after the procedure if renal function has not deteriorated
☐ Do not know
If other please specify _____

PART C

1. Do you think that in general the published guidelines are clear?
☐ Yes
☐ No
☐ Don't know

2. a) Do you think that it makes any difference to outcome if metformin isn't discontinued?
☐ Yes
If yes, what difference? _____
☐ No
☐ Don't know

b) If yes, what is the likely adverse outcome?

c) Is the adverse outcome reversible?
☐ Yes
☐ No
☐ Don't know

3. a) Do you think that clearer guidance is needed?
☐ Yes
☐ No
☐ Don't know

b) If yes, what form should it take?

4. What % of participants in this audit do you think are following guidelines?
☐ >90%
☐ >75%
☐ <50%
☐ <25%

was that, when specifically asked, many (43%) did not think that any of the various current guidelines were clear, and overall (62%) of respondents felt that clearer guidance was needed. Our study of current practice on the management of patients on metformin undergoing coronary interventions demonstrated wide variations in clinician uptake and implementation of guidelines and overall clinical practice on a national scale.

Inconsistencies in existing guidelines

Current guidelines are inconsistent in their recommendations on the need to discontinue metformin, the timing of its cessation and the need to retest renal function prior to restarting metformin[15]. These inconsistencies are partly due to poor available evidence underpinning the guideline recommendations. It could of course be that the clinical issue is less important than believed by some, leading to

Table 4. Timing of metformin cessation and restarting of metformin, by respondents, around the time of coronary angiography.

	On the day of the procedure (% of respondents)	24 hours (% of respondents)	48 hours (% of respondents)	>48 hours (% of respondents)	Other (% of respondents)
Timing of metformin cessation prior to procedure	28	17	45	9	1a
Timing of restarting metformin if renal function is stable	0	17	63	19	1b

a: Cessation of metformin 48 hours before the procedure if abnormal renal function, and on the day of the procedure if renal function is normal; b: Do not know timing of restarting metformin

inconsistency. However, the weak evidence base available raises the question of how to develop guidelines in the absence of good quality evidence and whether consensus-based expert opinion is robust enough and should have a role in such a setting. The ACC/AHA/SCAI statement on PCI in patients on metformin[28] **(Table 2)** is derived from expert consensus, however it is referenced with a single citation on biguanide-related lactic acidosis by Aguilar et al[34] from 1992. This was a retrospective observational cohort study, which concluded that biguanides in general are not associated with a high risk of metabolic acidosis and that severe systemic dysfunction in diabetics is the main determinant for lactic acidosis. Such consensus-based guidelines may not be as highly regarded as robust evidence emanating from randomised clinical trials, and therefore may not be rigorously followed in clinical practice, leading to variations in management. It may be that clinicians "recognise" that the risk of M-ALA is low, and may therefore not adhere rigorously to published guidelines on metformin discontinuation in patients requiring coronary interventions. If an adverse outcome is rare and unlikely to occur, the guidelines are less likely to be widely adhered to in clinical practice.

Recommendations

Following review of the guidelines for metformin discontinuation in the setting of elective coronary intervention, and in view of the lack of robust evidence, we would recommend metformin discontinuation when:

1) Serum creatinine is above the normal range prior to coronary intervention;
2) If this is the case, withdraw metformin for 48 hours before contrast administration and only restart metformin, if renal function measured 48 hours after contrast administration has not deteriorated.

If a patient with renal impairment has taken metformin within 48 hours before contrast administration, the decision to postpone the procedure should be considered in the context of the urgency of the procedure, and after discussion with renal physicians. It is the authors' opinion that if coronary intervention is required, and in the absence of definitive evidence of harm, the procedure should take place with adequate hydration and intravenous fluids, to minimise the risk of renal failure. Consensus through the appropriate guideline bodies and regulatory agencies would be needed to endorse such recommendations. Adequately-sized trials with sufficient power to detect a significant difference are clearly needed.

Conclusion

In summary, review of the published data addressing the discontinuation of metformin for cardiac interventional procedures and a live snapshot of UK clinical practice has highlighted that robust evidence for M-ALA in diabetics on metformin undergoing coronary intervention is lacking. Existing guidelines on the management of such patients are inconsistent in their recommendations on the need to discontinue metformin, the timing of its cessation and the need to re-test renal function prior to recommencing metformin. Additionally, current practice varies widely. New data is necessary to determine whether there is a significant problem with lactic acidosis in those patients on metformin who undergo coronary angiography, and if so its scale. Furthermore, more data is needed to establish the potential hazard of inappropriate metformin discontinuation.

Conflict of interest statement

The authors have no conflict of interest to declare.

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