PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2013; **22**: 1027–1035
Published online 19 August 2013 in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.3501

REVIEW

Metformin therapy and kidney disease: a review of guidelines and proposals for metformin withdrawal around the world

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ABSTRACT

Objective We compared and contrasted guidelines on metformin treatment in patients with chronic kidney disease (CKD) around the world, with the aim of helping physicians to refine their analysis of the available evidence before deciding whether to continue or withdraw this drug.
Methods We performed a systematic research for metformin contraindications in: (i) official documents from the world's 20 most populated countries and the 20 most scientifically productive countries in the field of diabetology and (ii) publications referenced in electronic databases from 1990 onwards.
Results We identified three international guidelines, 31 national guidelines, and 20 proposals in the scientific literature. The criteria for metformin withdrawal were (i) mainly qualitative in the most populated countries; (ii) mainly quantitative in the most scientifically productive countries (with, in all cases, a suggested threshold for withdrawing metformin); and (iii) quantitative in all, but one of the literature proposals, with a threshold for withdrawal in most cases ($n = 17$) and/or adjustment of the metformin dose as a function of renal status ($n = 8$). There was a good degree of consensus on serum creatinine thresholds; whereas guidelines based on estimated glomerular filtration rate thresholds varied from 60 mL/minute/1.73 m^2 up to stage 5 CKD. Only one of the proposals has been tested in a prospective study.
Conclusions In general, proposals for continuing or stopping metformin therapy in CKD involve a threshold (whether based on serum creatinine or estimated glomerular filtration rate) rather than the dose adjustment as a function of renal status (in stable patients) performed for other drugs excreted by the kidney. Copyright © 2013 John Wiley & Sons, Ltd.

KEY WORDS—Type 2 diabetes; metformin; kidney disease; drug accumulation; lactic acidosis; pharmacoepidemiology

Received 25 April 2013; Revised 9 July 2013; Accepted 25 July 2013

INTRODUCTION

Metformin is recognized worldwide as having a pivotal role in the primary treatment of type II diabetes mellitus. However, there is still a debate concerning the drug's beneficial and adverse effects—particularly in terms of the high proportion of patients presenting with established or suspected kidney disease. Even though a critical review of the literature in this field has questioned the claimed danger of lactic acidosis in metformin-treated patients,[1,2] the latter context still influences treatment strategies.

Here, we compare and contrast official and literature-based guidelines on the metformin treatment of type II diabetes mellitus patients with chronic kidney disease (CKD) and critically analyse the selected criteria for drug withdrawal. Our objective was to help physicians to refine their analysis of the available evidence before deciding whether to continue or withdraw metformin therapy in CKD patients (in compliance with their locally applicable regulatory and legislative framework).

RESEARCH DESIGN AND METHODS

Data sources

We selected three different data sources:
- official documents from the world's 20 most populated countries in 2012.[3]
- official documents from the world's top 20 countries according to the International Science Ranking in the field of diabetology in 2012.[4]
- the scientific literature.

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Data selection

We performed a systematic Internet search for official documents on metformin contraindication in national formularies and official guidelines and (if the latter documents did not provide eligible data) websites, reference textbooks, marketing authorizations, or documents issued by diabetes associations. For the scientific literature, we identified proposals for metformin withdrawal by searching the MEDLINE, SCOPUS, and SCIENCE DIRECT electronic databases with the keywords "metformin", "contraindications", "renal failure", "chronic kidney disease", and "acute kidney failure".

Our search included English-language and non-English-language documents for national guidelines and English-language documents for literature proposals.

We chose a start date of 1990, which corresponds to the year in which the results of the first prospective study using metformin in (elderly) CKD patients were published.[5]

Data extraction

We reviewed the retrieved documents and publications and extracted criteria (whether qualitative and/or quantitative) for metformin withdrawal in CKD. For qualitative criteria, we cite the original wording or (for non-English-language documents) a translation.

RESULTS

We identified three international guidelines, 31 national guidelines, and 20 literature proposals. The collected data are presented by source in Tables 1–3[5–58] and are summarized in Table 4.

The criteria for metformin withdrawal were (i) mainly qualitative in the most populated countries; (ii) mainly quantitative in the most scientifically productive countries (with, in all cases, a suggested threshold for withdrawing metformin—mostly based on serum creatinine values); and (iii) quantitative in all but one of the literature proposals, with a threshold for withdrawal in most cases (in 17 of the 54 study documents) and/or an adjustment of the metformin dose as a function of renal status (in eight documents).

There was a good degree of consensus on serum creatinine thresholds (generally $\geq$1.5 mg/dL in men and $\geq$ 1.4 mg/dL in women). In contrast, estimated glomerular filtration rate (eGFR) thresholds varied from 60 mL/minute/1.73 m^2 up to stage 5 CKD (although most were at 30 mL/minute/1.73 m^2).

Literature proposals were the only one to suggest metformin dose adjustment as a function of renal status ($n = 8$). Two of the latter based their recommendation on measurement of the blood metformin level. Only one proposal for adjustment was based on a prospective study in CKD (a 2-month treatment study of elderly subjects, published in 1990[5]). Lastly, the criterion for CKD stability was only mentioned once (in a publication dating from 1995[40]).

DISCUSSION

Given that (i) the kidney clears metformin (in an unmodified form) from the blood about four to five times more quickly than it does creatinine and (ii) metformin accumulation has been associated with lactic acidosis (even though the occurrence of truly metformin-induced lactic acidosis is rare, and the supposed mortality rate in this context has been questioned[2]), it is not surprising that contraindications for the drug mainly refer to renal function.

The contraindications in the most populated countries (accounting for a large proportion of the world's diabetics) are mainly qualitative. Quantitative guidelines have traditionally been based on threshold values—particularly for serum creatinine (typically $>$1.5 mg/dL in men and 1.4 mg/dL in women). It is noteworthy that none of the analyzed documents mentioned the possibility of transient metformin withdrawal following the occurrence of events likely to induce acute changes in renal function (such as vomiting, dehydration, diarrhoea and so on) in general and in the elderly in particular.

With the view to better assessment of renal function, the literature proposals generally suggested replacing serum creatinine levels by the (eGFR, determined using the abbreviated modified diet in renal disease equation). Furthermore, one-third of the literature proposals featured a metformin dose adjustment (to suit the patient's renal status) rather than a threshold value for withdrawal. This reasoning was based on blood metformin assays in just a few publications and based only once on a prospective study of a 2-month course of metformin in elderly patients with CKD (published in 1990, i.e., the oldest publication considered here).[5] As expected, mean plasma metformin concentrations remained within normal values when subjects were given either 1700 mg per day of metformin for creatinine clearances above 60 ml/minute or 850 mg per day for clearances between 30 and 60 ml/minute. There was no statistically significant difference in plasma metformin concentration between the two dosage groups. Only the second oldest scientific article (published in 1995) mentioned that the stability of CKD was a criterion in the continuation or withdrawal of metformin therapy in CKD.[40]

DOI: 10.1002/pds

Table 1. Thresholds for guiding metformin withdrawal: official documents from the world's 20 most populated countries

	Country	Year	Ref.	Organization	National formularies, official guidelines, websites, reference textbooks, marketing authorizations, or documents issued by diabetes associations	Criterion	Threshold for withdrawing metformin
1	China	2005	6	Asian-Pacific Type 2 Diabetes Policy Group	Type 2 Diabetes Practical Targets and Treatments http://www.idf.org/	Serum creatinine	>150 μmol/L
		2010	7	—	China National Formulary 2010	Qualitative	"Abnormal kidney dysfunction" or "creatinine clearance rate"
2	India	2005	8	The Indian Council of Medical Research	ICMR Guidelines for Management of T2 Diabetes http://icmr.nic.in	Qualitative	"Renal insufficiency"
		2011	9	The National Rural Health Mission, Health & F.W. Department	Standard Treatment Guideline & Essential Medicine List (For Pregnant Women) http://nrhmorissa.gov.in	Qualitative	"Presence of renal disease"
		2012	10	Indian diabetes association	The Management Of The Metabolic Syndrome: An Indian Scenario http://www.diabetesindia.com	Qualitative	Not stated
3	USA	2008	11	US Food and Drug Administration	NDA 20-357/S-031 and NDA 21-202/S-016	Serum creatinine	Male: ≥1.5 mg/dL (>135 μmol/L) Female: ≥1.4 mg/dL (>110 μmol/L)
		2009	12	American Diabetes Association	A consensus statement of the American Diabetes Association	Qualitative	Renal dysfunction
		2012	13	American Diabetes Association	Position Statement of the American Diabetes Association	Serum creatinine	Male: ≥1.5 mg/dL Female: ≥1.4 mg/dL
		2012	14	US National Kidney Foundation	Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease, Guideline 2 http://www.kidney.org	Serum creatinine	Male: ≥1.5 mg/dL Female: ≥1.4 mg/dL
4	Indonesia	2000	15	Indonesian Diabetes Association	The epidemiology and management of diabetes mellitus in Indonesia	Qualitative	"Severe renal dysfunction"
		2005	16	International Diabetes Federation	Global Guideline for Type 2 Diabetes "Version for Indonesia" http://www.idf.org	Qualitative	"Evidence or risk of renal impairment"
		2005	6	Asian-Pacific Type 2 Diabetes Policy Group	Type 2 Diabetes Practical Targets and Treatments http://www.idf.org/	Serum creatinine	>150 μmol/L
5	Brazil	2010	17	Medical associations of Latin American countries	Consensus statement	eGFR	<30 mL/minute/1.73 m^2
6	Pakistan	2012	18	Pakistan Diabetes Institute	Guidelines for Management of Diabetes Mellitus http://www.diabetespakistan.com/	Qualitative	"Impaired renal function"
7	Nigeria	2012	19	Unofficial drug information website	Metformin HCl webpage http://niger-gouv.org/medicaments/	Serum creatinine	Male: ≥1.5 mg/dL Female: ≥1.4 mg/dL
8	Russia	2005	16	International Diabetes Federation	Global Guideline for Type 2 Diabetes "Version for Russia" http://www.idf.org	Qualitative	"Evidence or risk of renal impairment"
		2011	20	Russian Diabetes Federation	Metformin profile in "Diabetes", the journal of the Russian Diabetes Federation http://www.rda.org.ru/	Qualitative	"Renal failure"
		2012	21	Russian encyclopaedia of drugs and pharmacy products	http://www.rlsnet.ru/	Qualitative	"Renal impairment"
9	Bangladesh	2003	22	Bangladesh Institute Of Research and Rehabilitation for Diabetes Endocrine and Metabolic Disorders	Guidelines for care of type 2 diabetes mellitus in Bangladesh	Serum creatinine	≥2.5 mg/dL
10	Japan	2005	6	Asian-Pacific Type 2 Diabetes Policy Group	Type 2 Diabetes Practical Targets and Treatments http://www.idf.org/	Serum creatinine	>150 μmol/L
		2012	23	Japan pharmaceutical and medical device agency	Metformin HCl properties webpage http://www.info.pmda.go.jp	Qualitative	"Renal dysfunction (including mild failure)"
11	Mexico	2010	17	Medical associations of Latin American countries	Consensus statement	eGFR	<30 mL/minute/1.73 m^2
12	Philippines	2005	6	Asian-Pacific Type 2 Diabetes Policy Group	Type 2 Diabetes Practical Targets and Treatments http://www.idf.org/	Serum creatinine	>150 μmol/L

(*Continues*)

DOI: 10.1002/pds

Table 1. (Continued)

	Country	Year	Ref.	Organization	National formularies, official guidelines, websites, reference textbooks, marketing authorizations, or documents issued by diabetes associations	Criterion	Threshold for withdrawing metformin
		2006	[24]	—	Philippine National Formulary	Qualitative	"Renal impairment"
13	Vietnam	2005	[6]	Asian-Pacific Type 2 Diabetes Policy Group	Type 2 Diabetes Practical Targets and Treatments http://www.idf.org/	Serum creatinine	>150 µmol/L
14	Ethiopia	2008	[25]	—	Ethiopian National Drug Formulary	Qualitative	"Renal impairment"
		2010	[26]	Drug Administration and Control Authority of Ethiopia	Standard treatment guideline for general hospitals http://apps.who.int	Qualitative	"Renal diseases"
15	Egypt	2007	[27]	—	Egyptian National Formulary	Qualitative	"Renal failure"
16	Germany	2001	[28]	European Medicines Agency	CPMP/4082/00	Serum creatinine	Male: ≥1.5 mg/dL (>135 µmol/L) Female: ≥1.4 mg/dL (>110 µmol/L)
17	Iran	2011	[29]	—	Iranian Physician Desk Reference	Serum creatinine	Male: ≥1.5 mg/dL Female: ≥1.4 mg/dL
		2012	[30]	Iranian Drug and Poison Information Center website	Metformin HCl properties webpage http://www.darooyab.ir	Qualitative	"Renal disease"
18	Turkey	2005	[16]	International Diabetes Federation	Global Guideline for Type 2 Diabetes "Version for Turkey" http://www.idf.org	Qualitative	"Evidence or risk of renal impairment"
19	Congo	2012	[31]	"Diabaction-Congo "	Congo Diabetes Association guideline	Serum creatinine	Male: ≥1.5 mg/dL Female: ≥1.4 mg/dL
20	Thailand	2005	[6]	Asian-Pacific Type 2 Diabetes Policy Group	Type 2 Diabetes Practical Targets and Treatments http://www.idf.org/	Serum creatinine	>150 µmol/L

It appears thus that official guidelines and literature proposals differ in terms of both their nature (qualitative vs. quantitative) and, for quantitative guidelines, their approach (i.e., a threshold for withdrawal vs. dose adjustment). Whereas the serum creatinine threshold for withdrawing metformin treatment is relatively unequivocal (generally $\geq$1.5 mg/dL in men and $\geq$1.4 mg/dL in women), that of eGFR varies from $<$60–$<$15 mL/minute/1.73 m^2 (i.e., from stages 3–5 CKD). A threshold of 30 mL/minute/1.73 m^2 was, however, most frequently suggested. In line with our first contribution in this debate,[5] we continue to contest the validity of defining a threshold (whether based on serum creatinine or eGFR) for continuing or withdrawing metformin therapy. In fact, that amounts to saying "either the usual dose or not at all". In contrast, the reasoning for any drug excreted by the kidney should be to adjust the dose to the patient's renal status. For examples, the appropriate starting dose of aminoglycosides is based on serum creatinine levels and the calculated creatinine clearance rate. In other words, we believe that it is possible to continue metformin therapy as long as the dosage is adjusted to match the extent of renal impairment and for as long as renal function remains stable.

Whereas prophylactic measurement of kidney function are mainly used as a guide to initiating metformin treatment, it is noteworthy that lactic acidosis due to metformin occurs more frequently in acute kidney failure (because of cardiovascular failure, septic or haemorrhagic shock, etc.). In the largest series of metformin-treated patients with lactic acidosis yet reported, acute kidney failure appeared to be about three times more frequent than chronic kidney failure.[59]

Although precautions for metformin use are principally related to renal function, it is also surprising that little attention is paid to liver failure in general and cirrhosis in particular. It is well known that the liver has a key role in lactate clearance.[60] Indeed, severe liver failure is the sole exception to the rule in terms of a good prognosis in so-called metformin-associated lactic acidosis. In our experience of the latter condition, liver failure was the second most predominant feature of organ failure and the prime factor in terms of mortality (eight out of 12 patients).[60] Interestingly, the only biochemical parameter associated with a fatal outcome in two other series[61,62] was the initial prothrombin time.[63] In other words, renal dysfunction is only a prerequisite for metformin accumulation, but the latter is only dangerous *per se* when combined with liver failure.

DOI: 10.1002/pds

Table 2. Thresholds for guiding metformin withdrawal: official documents from the 20 top countries (according to the International Science Ranking) in the field of diabetology

	Country	Year	Ref.	Organization	National formularies, official guidelines, websites, reference textbooks, marketing authorizations, or documents issued by diabetes associations	Criterion	Threshold for withdrawing metformin
1	USA: cf. Table 1						
2	UK	2009	[32]	National Institute for Health and Clinical Excellence	The Management of Type 2 Diabetes: NICE Clinical Guideline 87 http://www.nice.org.uk	eGFR	<30 mL/minute/1.73 m^2
		2011	[33]	—	British National Formulary	eGFR	<30 mL/minute/1.73 m^2
3	Germany: cf. Table 1						
4	Italy: cf. Germany in Table 1 (European Medicines Agency)						
5	France: cf. Germany in Table 1 (European Medicines Agency) until 2012 (with new recommendations in 2013*)						
6	Japan: cf. Table 1						
7	Spain: cf. Germany in Table 1 (European Medicines Agency)						
8	Canada	2008	[34]	Canadian Diabetes Association	Clinical Practice Guidelines for the Prevention and Management of Diabetes	eGFR	<30 mL/minute/1.73 m^2
		2009	[35]	The Canadian Pharmacists Association	Practical Guideline: Pharmacologic management of type 2 diabetes	eGFR	<30 mL/minute/1.73 m^2
		2010	[36]	British Colombia Advisory Committee	Guidelines &Protocols for Diabetes Care www.bcguidelines.ca	eGFR	<30 mL/minute/1.73 m^2
9	Netherlands: cf. Germany in Table 1 (European Medicines Agency)						
10	Sweden: cf. Germany in Table 1 (European Medicines Agency)						
11	Australia	2005	[6]	Asian-Pacific Type 2 Diabetes Policy Group	Type 2 Diabetes Practical Targets and Treatments http://www.idf.org/	Serum creatinine	>150 µmol/L
		2009	[37]	Australian National Health and Medical Research Council	National Evidence Based Guideline for Blood Glucose Control in Type 2 Diabetes	eGFR	<30 mL/minute/1.73 m^2
		2012	[38]	Australian Therapeutic Goods Administration	Summary of product characteristics (SPC/RCP)	Creatinine clearance	<60 mL/minute
12	Denmark: cf. Germany in Table 1 (European Medicines Agency)						
13	Brazil: cf. Table 1						
14	China: cf. Table 1						
15	Poland: cf. Germany in Table 1 (European Medicines Agency)						
16	Switzerland	2012	[39]	Compendium Switzerland	Metformin HCl webpage http://www.kompendium.ch	Creatinine clearance	<60 mL/minute
17	Finland: cf. Germany in Table 1 (European Medicines Agency)						
18	Belgium: cf. Germany in Table 1 (European Medicines Agency)						
19	India: cf. Table 1						
20	Turkey: cf. Table 1						

*Caution for patients with creatinine clearance between 60 and 30 ml/minute/1.73 m^2, using a maximal metformin dose of 1500 mg per day.

DOI: 10.1002/pds

Table 3. Thresholds for guiding metformin withdrawal: proposals from the scientific literature

Year	Author	Ref.	Basis for proposal	Blood metformin measurement	Criterion	Threshold for withdrawing metformin	Metformin dose adjustment
1990	Lalau	[5]	Prospective 2-month study in the elderly: no difference in plasma metformin concentration between patients with metformin 1700 mg/day and creatinine clearance > 60 ml/minute, and those with 850 mg/day and 30–60 ml/minute clearance.	Yes	Creatinine clearance	No	Clearance >60: 1700 mg/day Clearance 30–60: 850 mg/day
1995	Sambol	[40]	Administration a single 850-mg oral dose of metformin in healthy subjects and 15 subjects with CKD ("mild to severe")	Yes	Qualitative	Moderate–severe CKD and unstable mild CKD	Reduction of around a third of the dose in the elderly and in patients with stable, mild CKD
2003	Jones	[41]	Personal suggestion, not based on a study	No	Serum creatinine	>150 µmol/L	No
2004	Nisbet	[42]	Personal suggestion, not based on a study	No	Creatinine clearance	<30 ml/minute	No
2005	McCormack	[43]	Personal suggestion, not based on a study	No	Creatinine clearance	No	A ~50% decrease in the maximum metformin dose for a creatinine clearance < 60 mL/minute
2007	Shaw	[44]	Personal suggestion to convert serum creatinine to eGFR, not based on a study	No	eGFR	eGFR < 30 ml/minute/1.73 m^2	No
2007	Warren	[45]	Personal suggestion to convert serum creatinine to eGFR, not based on a study	No	eGFR	<36–40 ml/minute/1.73 m^2	No
2008	Herrington	[46]	Personal suggestion, not based on a study	No	eGFR	<30 ml/minute/1.73 m^2	GFR 90–60 in patients aged over 70 years: reduce by half. GFR < 60 ml/minute: reduction again by half
2009	Haneda	[47]	Personal suggestion, not based on a study	No	eGFR	<60 ml/minute/1.73 m^2	No
2009	Mani	[48]	Personal suggestion, not based on a study	No	eGFR	Stage 5 CKD (<15 ml/minute/1.73 m^2)	No
2010	Chen	[49]	Personal suggestion, not based on a study	No	eGFR	<40 ml/minute/1.73 m^2	No

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2010	Frid	[50]	Metformin measurement in plasma: "patients above the limit of GFR proposed in NICE rarely had metformin levels above presumed upper therapeutic limit"	Yes	eGFR	<30 ml/minute/1.73 m^2	No
2010	Hartmann	[51]	Personal suggestion, not based on a study	No	eGFR	<60 ml/minute/1.73 m^2	No
2010	Vasisht	[52]	Personal suggestion to convert serum creatinine to eGFR, not based on a study	No	eGFR	<60 ml/minute/1.73 m^2	No
2011	Graham	[53]	Personal suggestion, not based on a study	No	Creatinine clearance	No	The initial maximum target dose of 1500 mg/day if creatinine clearance is ~ 60 mL/minute. The started dosage should be commenced at a lower level of clearance and 750 mg/day if creatinine clearance ~ 30 mL/minute. GFR ≥ 90: 2500 mg/day GFR ≥ 60: 2000 mg/day GFR ≥ 45: 1000 mg/day GFR ≥ 30: 500 mg/day GFR ≥ 60: no contraindication GFR < 60 ≥ 45: increased monitoring of renal function GFR < 45 ≥ 30: decrease the dose by 50% or use the half-maximum dose
2011	Klachko	[54]	Personal suggestion, not based on a study	No	eGFR	<30 ml/minute/1.73 m^2	
2011	Lipska	[55]	Personal suggestion, not based on a study	No	eGFR	<30 ml/minute/1.73 m^2	
2012	Duong	[56]	Metformin levels in 24 stages 3–5 CKD patients (of whom two were on dialysis), compared with healthy subjects	Yes	Creatinine clearance	<20 ml/minute	No
2012	Martínez-Castelao	[57]	Personal suggestion, not based on a study	No	eGFR	<30 ml/minute/1.73 m^2 (<45 ml/minute/1.73 m^2 in patients at risk for lactic acidosis)	No
2012	Zanchi	[58]	Personal suggestion, not based on a study	No	eGFR	<45 ml/minute/1.73 m^2	Proposed adjustment according to renal function at least once a year in patients already on metformin and with a GFR 45–60 ml/minute

DOI: 10.1002/pds

Table 4. Summary of the available data according to the nature of the source and the criteria for withdrawing metformin

Criteria			Guidelines from 20 most populated countries	Guidelines from 20 most scientifically productive countries	Proposals from scientific literature ($n = 20$)
Qualitative			19	6	1*
Quantitative	Threshold	Serum creatinine	14	16	1
		Creatinine clearance or eGFR	2	9	16†
	Adjustment	Serum creatinine	—	—	—
		Creatinine clearance or eGFR	—	—	7†

*Plus a proposal for adjustment of the metformin dose according to the CKD stage.
†A single proposal may include a threshold and/or a dose adjustment.

The present debate is of critical importance because the current contraindications for metformin exclude its use in a large proportion of patients with CKD (a proportion that is set to rise in view of the ageing and more fragile population). These patients run the risk of exposure to severe adverse events caused by the ill-judged replacement of metformin by other drugs (e.g., hypoglycaemia with sulfonylureas, insulin etc.) and may also suffer from the undue loss of metformin's beneficial effects.[64]

CONCLUSION

Guidelines for continuing or withdrawing metformin therapy in CKD are either qualitative or based on a threshold (typically serum creatinine or eGFR) and, in contrast to recommendations on other drugs excreted by the kidney, do not involve adjustment of the metformin dose as a function of renal status (in stable patients).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

KEY POINTS
- The criteria for metformin withdrawal are mainly qualitative in the most populated countries
- Quantitative criteria for metformin withdrawal are mostly based on serum creatinine values
- The current contraindications for metformin exclude its use in a large proportion of patients with CKD
- In contrast to recommendations on other drugs excreted by the kidney, guidelines do not involve adjustment of the metformin dose as a function of renal status.

REFERENCES

1. Lalau JD, Race JM. Lactic acidosis in metformin therapy: searching for a link with metformin in reports of 'metformin-associated lactic acidosis'. *Diabetes Obes Metab* 2001; **3**(3): 195–201.
2. Lalau JD. Lactic acidosis induced by metformin: incidence, management and prevention. *Drug Saf.* 2010; **33**(9): 727–740.
3. http://www.nationsonline.org/oneworld/world_population.htm [December 2012].
4. http://www.scimagojr.com/countryrank.php?area=2700&category=2712&region=all&year=all&order=it&min=0&min_type=it [December 2012].
5. Lalau JD, Vermersch A, Hary L, *et al*. Type 2 diabetes in the elderly: an assessment of metformin (metformin in the elderly). *Int J Clin Pharmacol Ther Toxicol* 1990; **28**(8): 329–332.
6. Asian-Pacific Type 2 Diabetes Policy Group Type 2 Diabetes Practical Targets and Treatments http://www.idf.org/webdata/docs/T2D_practical_tt.pdf [December 2012].
7. China National Formulary 2010.
8. The National Rural Health Mission, Health & F.W. Department, Government of Odisha http://nrhmorissa.gov.in/jssk/pdf/StandardTreatmentandEssentialMedicineList.pdf [December 2012].
9. Indian diabetes association declaration; http://www.diabetesindia.com/diabetes/mets_impaired_glycemia.htm[December 2012].
10. http://icmr.nic.in/guidelines_diabetes/section7.pdf
11. Glucophage® leaflet approved by FDA 2008.
12. Nathan DM, Buse JB, Davidson MB, *et al*. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American diabetes association and the European association for the study of diabetes. *Diabetes Care* 2009; **32**(1): 193–203.
13. Inzucchi SE, Bergenstal RM, Buse JB, *et al*. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American diabetes association (ADA) and the European association for the study of diabetes (EASD). *Diabetologia* 2012; **55**(6): 1577–1596.
14. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease GUIDELINE 2; http://www.kidney.org/professionals/kdoqi/guideline_diabetes/guide2.htm [December 2012].
15. Sutanegara D, Budhiarta AA. The epidemiology and management of diabetes mellitus in Indonesia. *Diabetes Res Clin Pract* 2000; **50**(suppl 2): S9–S16.
16. International Diabetes Federation Global Guideline for Type 2 Diabetes 2005. http://www.idf.org/webdata/docs/IDF%20GGT2D.pdf [December 2012].
17. Guzmán JR, Lyra R, Aguilar-Salinas CA, *et al*. Treatment of type 2 diabetes in Latin America: a consensus statement by the medical associations of 17 Latin American countries. Latin American diabetes association. *Rev Panam Salud Publica* 2010; **28**(6): 463–471.
18. Guidelines for Management of Diabetes Mellitus of Diabetic's Institute Pakistan; http://sugartoday.info/?portfolio=oral-medication.
19. Nigerian Non official Drug Information website http://niger-gouv.org/medicaments/65862-008-metformin-hydrochloride.html [December 2012].
20. Russian Diabetes Federation. *Diabetes J*; **4**(5) / CD in February 2011 PI number FS77-40852 on 07/05/2010-http://rda.org.ru/doc/SD2_5_2011.pdf [January 2013].
21. Russian Encyclopaedia of Drugs and Pharmacy Products; http://www.rlsnet.ru/tn_index_id_7090.htm [January 2013].
22. Bangladesh Institute of Research and Rehabilitation for Diabetes Endocrine and Metabolic Disorders Guidelines for Care of Type 2 Diabetes Mellitus in Bangladesh 2003.
23. Japan pharmaceutical and medical device agency; Metformin HCl Properties Webpage; http://www.info.pmda.go.jp/go/pack/3962002F1080_1_10/ [January2013].

DOI: 10.1002/pds

24. Philippine National Formulary 2006.
25. Ethiopian National Drug Formulary 2008.
26. Drug Administrations and Control Authority of Ethiopia Contents. Standard Treatment Guideline for General Hospitals http://apps.who.int/medicinedocs/documents/s17822en/s17822en.pdf [January 2013].
27. Egyptian National Formulary 2007.
28. Metformin Summary Information - European Medicines Agency CPMP/4082/00.
29. Iranian Physician Desk Reference 2011.
30. http://www.darooyab.ir Persian Drug Information Site; http://www.darooyab.ir/DrugInfoD.aspx?MGID=NjQw [January 2013].
31. Congo Diabetes Association Diabaction-Congo declaration.
32. NICE. Type 2 Diabetes: The Management of Type 2 Diabetes: NICE Clinical Guideline 87. National Institute for Health and Clinical Excellence, 2009; http://www.nice.org.uk/nicemedia/live/12165/44320/44320.pdf [January 2013].
33. British National Formulary 2011.
34. *Can J Diabetes*. 2008 **32**(Suppl 1): S53–S61.
35. Pharmacologic management of type 2 diabetes. *Can Pharm J* 2009; **142**(Suppl 1): S19–S25.
36. British Colombia Advisory Committee for Guidelines & Protocols; www.bcguidelines.ca/pdf/diabetes.pdf [January 2013].
37. Colagiuri S, Dickinson S, Girgis S, Colagiuri R. National Evidence Based Guideline for Blood Glucose. Control in Type 2 Diabetes. Diabetes Australia and the NHMRC, Canberra 2009.
38. Metformin Approved Leaflet by TGA; https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-05648-3.
39. Metformin HCl properties webpage http://www.kompendium.ch/mpro/mnr/1943/html/fr#7200 [January 2013].
40. Sambol NC, Chiang J, Lin ET, *et al*. Kidney function and age are both predictors of pharmacokinetics of metformin. *J Clin Pharmacol* 1995; **35**(11): 1094–1102.
41. Jones GC, Macklin JP, Alexander WD. Contraindications to the use of metformin. Evidence suggests that it is time to amend the list. *BMJ* 2003; **326**(7379): 4–5.
42. Nisbet JC, Sturtevant JM, Prins JB. Metformin and serious adverse effects. *Med J Aust* 2004; **180**(2): 53–54.
43. McCormack J, Johns K, Tildesley H. Metformin's contraindications should be contraindicated. *CMAJ* 2005; **173**(5): 502–504.
44. Shaw JS, Wilmot RL, Kilpatrick ES. Establishing pragmatic estimated GFR thresholds to guide metformin prescribing. *Diabet Med* 2007; **24**(10): 1160–1163.
45. Warren RE, Strachan MW, Wild S, McKnight JA. Introducing estimated glomerular filtration rate (eGFR) into clinical practice in the UK: implications for the use of metformin. *Diabet Med* 2007; **24**(5): 494–497.
46. Herrington WG, Levy JB. Metformin: effective and safe in renal disease? *Int Urol Nephrol* 2008; **40**(2): 411–417.
47. Haneda M, Morikawa A. Which hypoglycaemic agents to use in type 2 diabetic subjects with CKD and how? *Nephrol Dial Transplant* 2009; **24**(2): 338–341.
48. Mani MK. Metformin in renal failure--weigh the evidence. *Nephrol Dial Transplant* 2009; **24**(7): 2287–2288.
49. Chen HS. Old age may not be a contraindication to the use of metformin. *J Chin Med Assoc* 2010; **73**(12): 615–616.
50. Frid A, Sterner GN, Löndahl M, *et al*. Novel assay of metformin levels in patients with type 2 diabetes and varying levels of renal function: clinical recommendations. *Diabetes Care*. 2010; **33**(6): 1291–1293.
51. Hartmann B, Czock D, Keller F. Drug therapy in patients with chronic renal failure. *Dtsch Arztebl Int* 2010; **107**(37): 647–655.
52. Vasisht KP, Chen SC, Peng Y, *et al*. Limitations of metformin use in patients with kidney disease: are they warranted? *Diabetes Obes Metab* 2010; **12**(12): 1079–1083.
53. Graham GG, Punt J, Arora M, *et al*. Clinical pharmacokinetics of metformin. *Clin Pharmacokinet* 2011; **50**(2): 81–98.
54. Klachko D, Whaley-Connell A. Use of metformin in patients with kidney and cardiovascular diseases. *Cardiorenal Med* 2011; **1**(2): 87–95.
55. Lipska KJ, Bailey CJ, Inzucchi SE. Use of metformin in the setting of mild-to-moderate renal insufficiency. *Diabetes Care* 2011; **34**(6): 1431–1437.
56. Duong JK, Roberts DM, Furlong TJ, *et al*. Metformin therapy in patients with chronic kidney disease. *Diabetes Obes Metab* 2012; **14**(10): 963–965.
57. Martínez-Castelao A, Górriz JL, Sola E, *et al*. About the discrepancies between consensus documents, clinical practice guidelines, and legal regulations in the treatment of type 2 diabetes. *Nefrologia* 2012; **32**(4): 419–426.
58. Zanchi A, Lehmann R, Philippe J. Antidiabetic drugs and kidney disease--recommendations of the Swiss society for endocrinology and diabetology. *Swiss Med Wkly* 2012; **142**:w13629.
59. Lalau JD, Race JM. Lactic acidosis in metformin-treated patients. Prognostic value of arterial lactate levels and plasma metformin concentrations. *Drug Saf* 1999; **20**(4): 377–384.
60. Scheen A. Clinical pharmacokinetics of metformin. *Clin Pharmacokinet* 1996; **30**(5): 359–371.
61. Chan JCN, Davidons JA. Survival benefits of metformin in high-risk populations. In *Metformin: The Gold Standard*, Bailey CJ, Campbell IW, Chan JCN *et al*. (eds.). Wiley: Chichester: , 2007: 125–134.
62. Cohen R. Role of the liver and the kidney in acid–base regulation and its disorders. *Br J Anesthesiol* 1991; **67**(2): 154–164.
63. Seidowsky A, Nseir S, Houdret N, *et al*. Metformin-associated lactic acidosis: a prognosis and therapeutic study. *Crit Care Med* 2009; **37**(7): 2191–2196.
64. Kosmalski M, Drozdowska A, Sliwinska A, *et al*. Inappropriate metformin prescribing in elderly type 2 diabetes mellitus (T2DM) patients. *Adv Med Sci* 2012; **57**(1): 65–70.