Metformin and CKD – Really a Bad Idea?

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“Doctor, my diabetes is cured!”

- “Diabetic “Burn-Out” and the Kidney
  - Decreased renal and hepatic insulin clearance
  - Decreased renal gluconeogenesis
  - Decreased food intake / anorexia
  - Protein energy wasting
  - Hypoglycemic effect of dialysis

Diabetic Burn Out

- In CKD / Uremia, increased levels of guanidino compounds*
- This is, at least part of the phenomenon

*Aoyagi, K: Mol Cell Biochem 244: 11-15, 2003
Koppel, JD, et al.: J Lab Clin Med 90: 303-311, 1977
Stein, IM, et al: NEJM 280: 926-930, 1969

Guanidino Compounds and DM

- French Lilac used for diabetic “treatment” in medieval times*
  - Active ingredient guanidine
- Led to development of 3 Biguanides:
  - Phenformin
  - Buformin
  - Metformin

*Bailey CJ, Day C: Traditional plant medicines as treatments for diabetes. Diabetes Care 1989;12:553-564

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Metformin

- Therapy for DM since 1995
- 5th most prescribed drug in the US in 2016*
- “Sibling” of Phenformin / DBI

*www.lowestmed.com/top-50-prescription-drugs-filled/ June 16, 2016

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Metformin

- Pharmacology
  - Rapidly absorbed in small intestine*
  - Peak levels in 2 hours*
  - Filtered from glomerulus and secreted from tubule**
  - Clearance reduced by 75% in CKD 3***

*Graham GG, et al.: Clin Pharmacokinet 2011;50:81-98.
**Duong JK, et al.: Drug Saf 2013;36:733-746.
***Sambol NC, et al.: J Clin Pharmacol 1995;35:1094-1102

Metformin - Mechanism

- Inhibits hepatic gluconeogenesis*
- Augments insulin sensitivity*
- Increases insulin-mediated glucose uptake in periphery**
- Reduces free fatty acid substrate for gluconeogenesis**

*McIntyre HD, et al.: Aust N Z J Med 1991;21:714-719.
**Pernicova I, et al.: Nat Rev Endocrinol 2014;10:143-156.

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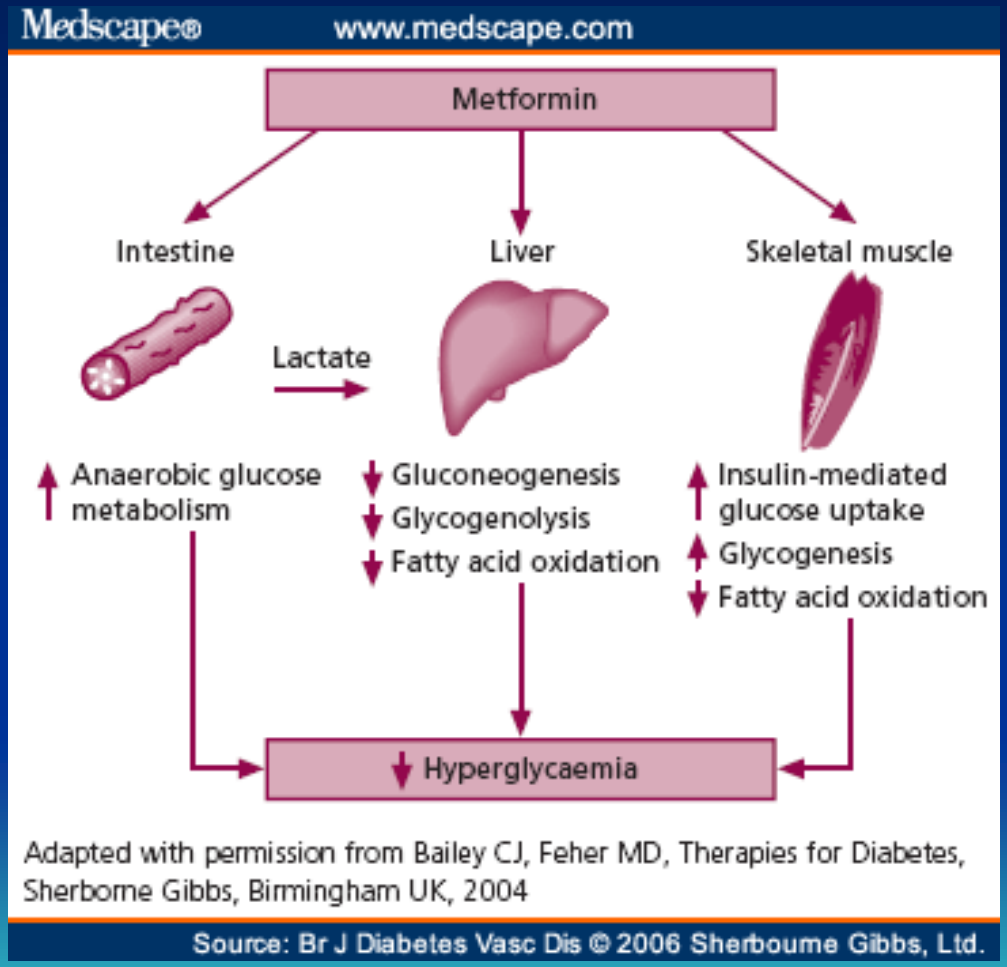
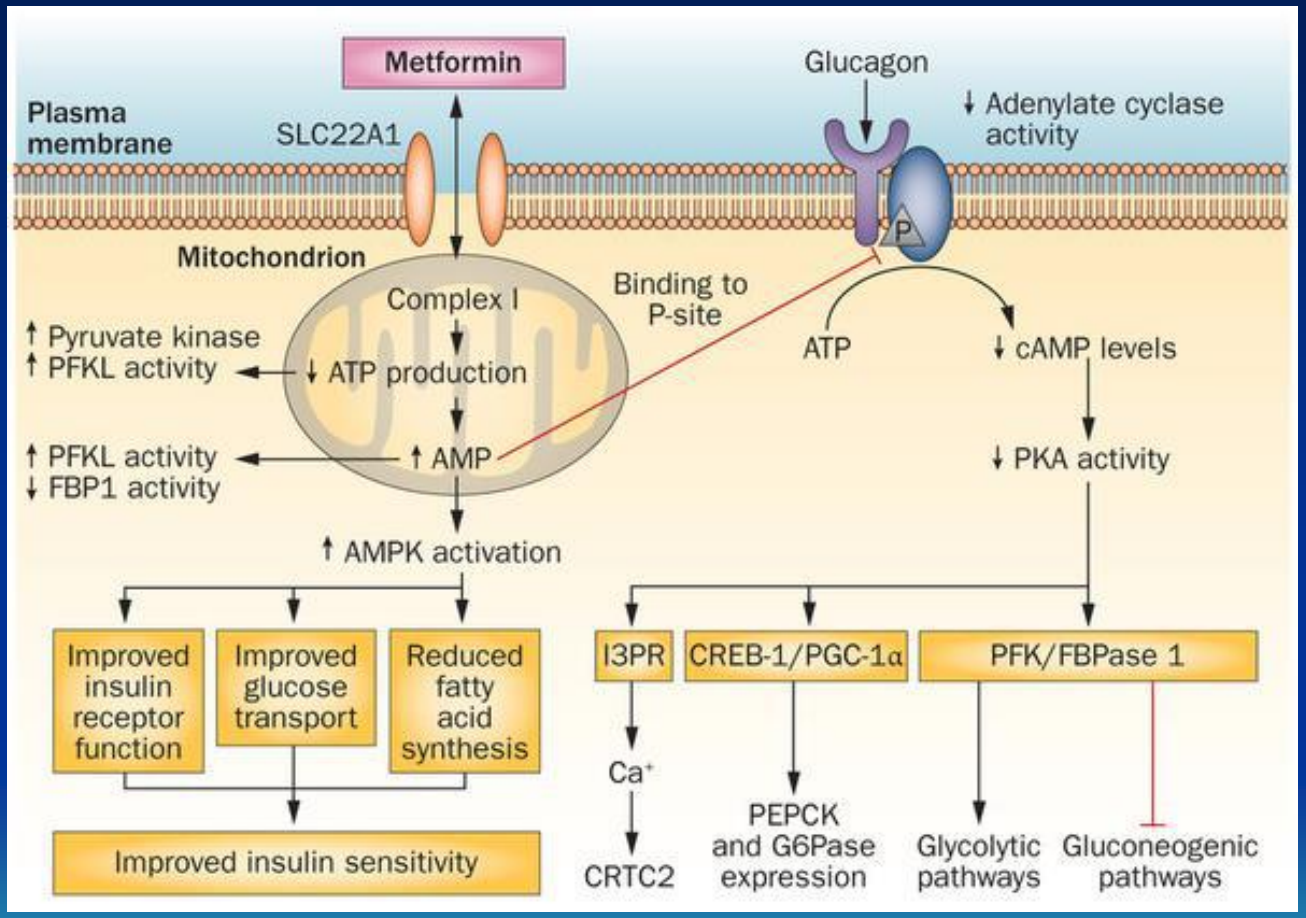
Metformin - Mechanism



Metformin - Mechanism



Pernicova, I and Korbonitz, M: Nat Rev Endocrinology 10: 143-156, 2014

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Metformin - Mechanism

- In essence, Metformin (and all of the Biguanides) “burns out” your diabetes just like in CKD……

Metformin Side Effects

- Diarrhea
- Vomiting
- Abdominal Pain
- Drowsiness
- Headache
- **Metformin Associated Lactic Acidosis –**
  - The most feared and perhaps least understood

Lactic Acidosis

- Divided Into 2 Categories*
  - Type A: Tissue hypo-perfusion / hypoxia
  - Type B: Not related to tissue hypoxia
- 1964
  - Broder and Weil report Lactate levels >4 associated with poor prognosis**

*Woods HFC, Robert . Clinical and biochemical aspects of lactic acidosis. Blackwell Scientific; Oxford: 1976.
**Science: 143(3613): 1457-1459, 1964

Lactic Acidosis – Causes*

- Shock
  - Distributive, Cardiogenic, Hypovolemic, Obstructive
- Post Cardiac Arrest
- Regional Tissue Ischemia
  - Mesenteric, Limbs, Burns, Trauma
- DKA

*Adapted from Andersen, LW, et al.: Mayo Clin Proc 88(10): 1127-1140, 2013

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Lactic Acidosis – Causes*

- Anaerobic Muscle Activity
- Thiamine Deficiency
- Liver Failure
- Malignancy
- Mitochondrial Disease

*Adapted from Andersen, LW, et al.: Mayo Clin Proc 88(10): 1127-1140, 2013

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Lactic Acidosis – Causes*

- Toxins / Drugs
  - Alcohol, Cocaine, Carbon Monoxide, Cyanide
- Pharmacological Agents
  - Linezolid, Reverse Transcriptase Agents, Epinephrine, Propofol, Acetaminophen, $Beta_2$ Agonists, Theophylline, **Phenformin**, **Metformin**

*Adapted from Andersen, LW, et al.: Mayo Clin Proc 88(10): 1127-1140, 2013

Phenformin

- High affinity for mitochondrial membranes
- Inhibits mitochondrial “respiration”
- Inhibits Lactate oxygenation
- Increases plasma Lactate concentration
- $t_{1/2}$ of 7 to 15 hours / Metabolized by liver
- Increased LA
  - **0.4 to 0.64 per 1,000 pt-years with mortality of 30 – 50 %**

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Phenformin vs. Metformin

- Metformin less affinity for mitochondrial membrane
- Less inhibition of mitochondrial respiration
- Not metabolized
- Shorter $t_{1/2}$ of 1.5 to 6.5 hours
- Lactic acidosis in **0.03 per 1000 pt-years**
- Reported cardiovascular benefit in CHF(?)

Phenformin vs. Metformin

- Metformin concentrates in the cytosol
  - Less effect on the mitochondria
  - Less protein binding
  - Shorter half-life than Phenformin,
- Therefore **Metformin causes less Lactic Acid formation than Phenformin.**

Phenformin vs. Metformin

	PHENFORMIN	METFORMIN
Affinity for membrane	+++	+
Inhibits Mito Respiration	++	+
Metabolized	Liver	Not metabolized
Inhibits Lactate oxygenation	+	
Increases Lactate	++	+
Half life	7 – 15 hours	1.5 to 6.5 hours
Lactic Acidosis	0.4 – 0.64 / 1000 pt-yr	0.03 / 1000 pt-yr
Other		?Cardiovascular benefit

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Mechanism of MALA

- Metformin selectively
  - Inhibits the mitochondrial glycerophosphate dehydrogenase
    - Which results in accumulation of NAD,
    - Which in turn inhibits conversion of lactate to pyruvate

Mechanism of MALA

- Lactate accumulation d/t:
  - Enhanced pyruvate production,
  - Reduced pyruvate conversion to CO_2 & H_2O
  - Altered mitochondrial redox state leading to increased lactate production
- **Metformin induced LA is type B**

Metformin Kinetics

- •Metformin plasma levels should not exceed 5mg/L
- •The therapeutic range for metformin is 0.7 to 5 mg/L

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MALA- Contributing Causes

- GI tract
  - Also has increased LA production
- Metformin accumulates in hepatocytes expressing an Organic Cation Transporter
  - Reduced liver uptake of LA
  - OCT knockout mice did not get LA

MALA- Contributing Causes

- Platelets
  - In Pigs, severe metformin intoxication causes mitochondrial dysfunction in platelets. As well as other vital organs like the heart, kidney and skeletal muscle.
  - Human platelets exposed to toxic dose of metformin, both in vitro and in vivo, have clear signs of mitochondrial dysfunction.

Protti et al. Crit Care 16(5), 2012

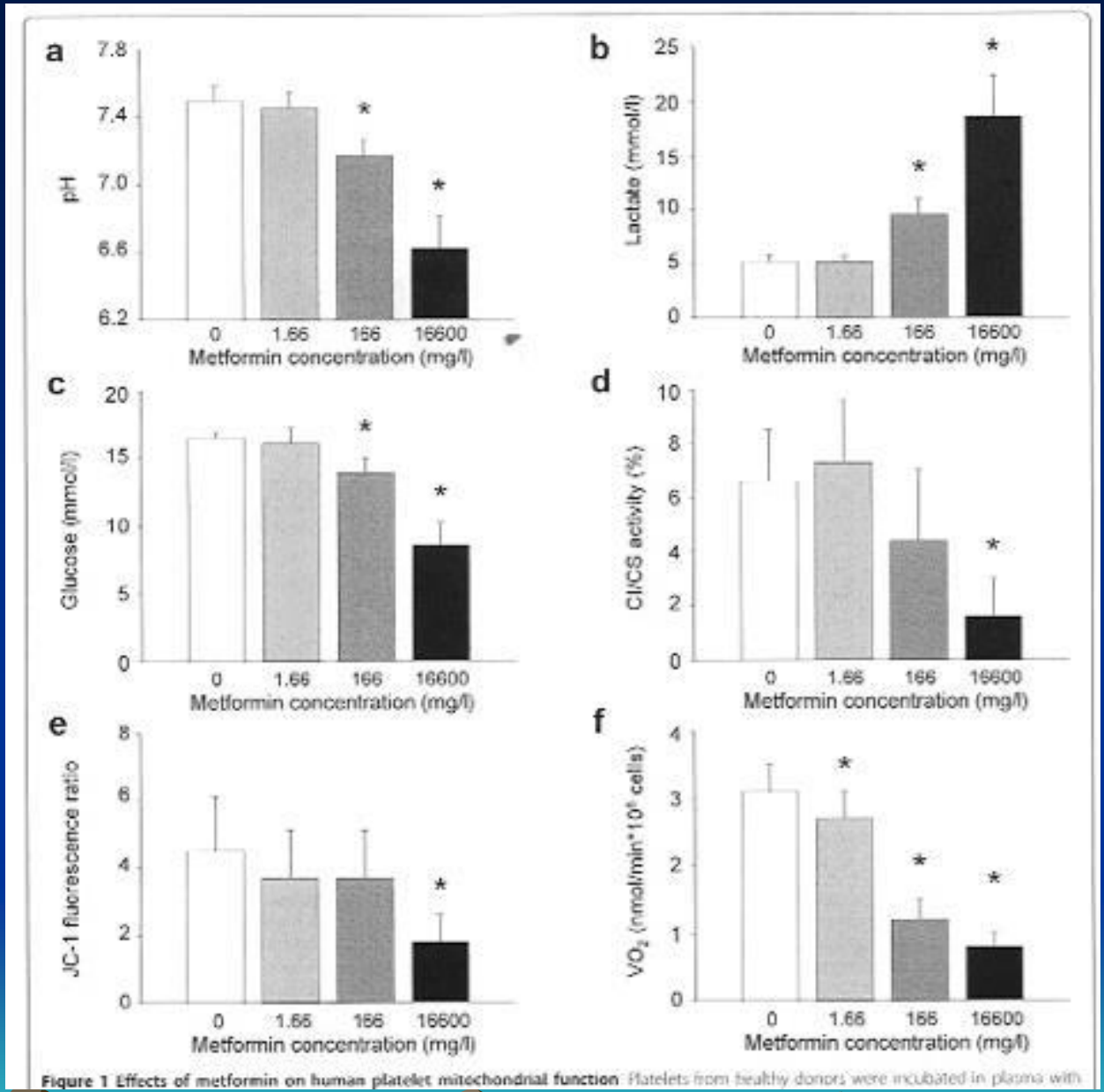

Figure 1 Effects of metformin on human platelet mitochondrial function Platelets from healthy donors were incubated in plasma with

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MALA – Contributing Causes

- Platelets
  - In vitro, Metformin increased Lactate production and Glucose consumption in human platelets
    - Dose and time dependent
    - Therapeutic doses do not alter human platelet mitochondrial function

Protti et al. Crit Care 16(5), 2012

Metformin, Mitochondria and LA

- Human platelet:
  - Decreased respiration during metformin-induced LA d/t drug accumulation, not circulatory collapse.
- Human RBCs (lack mitochondria)
  - No altered cellular metabolism with high doses of metformin.

Metformin, Mitochondria and LA

- If analogous changes occur in other organs, they will likely contribute to the pathogenesis of lactic acidosis.

So, is MALA Really an Issue?

- 3 to 9 cases per 100,000 patient- years receiving Metformin*
  - Similar to diabetic patients not receiving metformin**
- Metformin use has increased but LA has not***

*van Berlo-van de Laar, IR, et al. J Clin Pharm Ther 36(3): 376-382, 2011
**Salpeter SR, et al. Cochrane Database Syst Rev. 2006;1:CD002967
***Hamnvik OP, et al. Mt Sinai J Med. 2009;76:234-243.

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So, is it OK to use?

- A total of 194 studies from 1959 to 2002 reported no cases of LA
- The true incidence on a repeat investigation in 2010 calculated MALA to be < 4.2/100,000 patient-years

*Heaf, JG & van Biesen, W: Clinical Diabetes 29(3): 97-101, 2011

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So, is it OK to use?

Tabel 1. Epidemiology of Lactic Acidosis

Author	Location	Treatment	Year	Cases (*n*)	Patient-Years (*n*)	Incidence Per 100,000 Patient-Years
Brown[13]	United States	No biguanides	1993–1994	4(7)	41,426	9.7 (16.9)
Bergman[1]	Sweden	Metformin	1975–1977	2(3)	20,548	9.7 (14.6)
Wilholm[ ]	Sweden	Metformin	1977–1991	18	249,400	7.2
Stang[31]	Canada	Metformin	1080–1995	2	22,296	8.9
Misbin[32]	United States	Metformin	1995–1996	47	Approx. 1,000,000	4.7
Bodmer[15]	United States	Metformin Sulfonylurea	1994–2006	5	50,048	3.3 4.8
Aguilar[14]	Mexico	Metformin Sulfonylurea	1987–1990			0.0* 2.9*
Salpeter[18]	World	Metformin	1959–2002	0	36,893	0.0

*Data in parentheses indicate possible cases included. *Per 100 acute admissions.*

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So, is it OK to use?

- "…there is little, if any, theoretical justification for the claims that Metformin contributes to the incidence of LA and that epidemiological evidence is lacking. If there is any impact, it is probably rather low."*

*Heaf, JG & van Biesen, W: Clinical Diabetes 29(3): 97-101, 2011

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So, is it OK to use?

- “It is suggested that introduction of Metformin therapy to more advanced stages of CKD may bring therapeutic benefits that outweigh the possible risks.”*

*Heaf, J.: Peritoneal Dialysis International 34(4): 353-357, 2014

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So, is it OK to use?

- Meta-analysis in the UK
  - "…no clear effect of metformin on lactate levels was seen. Diabetes itself is a more important risk factor for LA…which occurs in association with acute illness. The current guidance adopts a cautious approach but may overemphasize the role of metformin in diabetic patient with LA."*

*Scale T & Harvey JN: Clinical Endocrinology, 74(2): 191–196, 2011

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So, is it OK to use?

- Retrospective review of all cases of LA at a single hospital*
  - "Considering specifically diabetic patients without cardiopulmonary insufficiency, lactate levels were slightly higher in patients with type 2 diabetes but there was no difference between those on metformin compared with diabetic patients not on metformin."

*Scale T & Harvey, JN: Clinical Endocrinology, 74 (2): 191-6, 2011

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So, is it OK to use?

- From the UK
  - "Diabetic patients without cardiopulmonary insufficiency, lactate levels were slightly higher in patients with type 2 diabetes but there was no difference between those on metformin compared with diabetic patients not on metformin."*

*Tahrani AA, et al. BMJ. 335 (7618): 508-512. Sept 8, 2007

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So, is it OK to use?

- From Grenoble – 302 cases of LA matched with 604 without LA over 4 years:
  - All patients with DM 2
  - "Metformin, compared with acute medical conditions, seemed not to be associated with LA with type 2 diabetes; however in case of AKI, metformin may be associated with LA."*

*Lepelley M, et al. J Diabetes Res, 2016

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So, is it OK to use?

- Meta-analysis of 347 trials:*
  - 70,490 patient-years with Metformin and 55,451 patient-years in non-metformin group
    - "There is no evidence to date that metformin therapy is associated with an increased risk of lactic acidosis or with increased levels of lactate compared with other anti-hyperglycemic treatments…if the drugs are prescribed under study conditions, taking into account contraindications."

*Salpeter SR, et al. Cochrane.org. April 14, 2010

And here's what's weirder…

- Heart failure had been a contraindication
  - Metformin patients show improved cardiac outcomes in patients with DM and CHF.
- No longer listed as a contraindication
- Is Metformin "good for you"?

Contraindications

- Impaired renal function (GFR < 45)
- Liver failure
- Severe hypoxia
- *Heart failure (No longer a contraindication)*
- Surgery
- Alcohol use

BUT……

But it's not OK to use

- Australia: Series of 10 patients with MALA
  - Higher rate of LA in patients on metformin
  - Significant increase risk of LA in Metformin patients compared to the general population
  - MALA leads to increased mortality but not as high as in LA associated with sepsis
  - Advise reduce dose of Metformin until GFR < 20, then to stop altogether

World Journal Nephrology 2016

But it's not OK to use

- Taiwan
  - Prior to restriction of Metformin in CKD patients, metformin users had a 29% higher mortality than nonusers over a 2 year period.
  - There was a dose dependent relationship between metformin and death.
  - Metformin users did have a 23% increased risk of LA, but did not correlate with death.

Metformin and AKI

- Metformin is eliminated rapidly and actively by the kidneys
- Any AKI may lead to metformin accumulation
- Higher levels Metformin associated with LA

Metformin and CKD

- Chicken vs Egg?
  - More MALA associated with AKI rather than CKD
  - But, those with CKD are at higher risk for AKI and therefore Metformin accumulation

A Perfect Storm

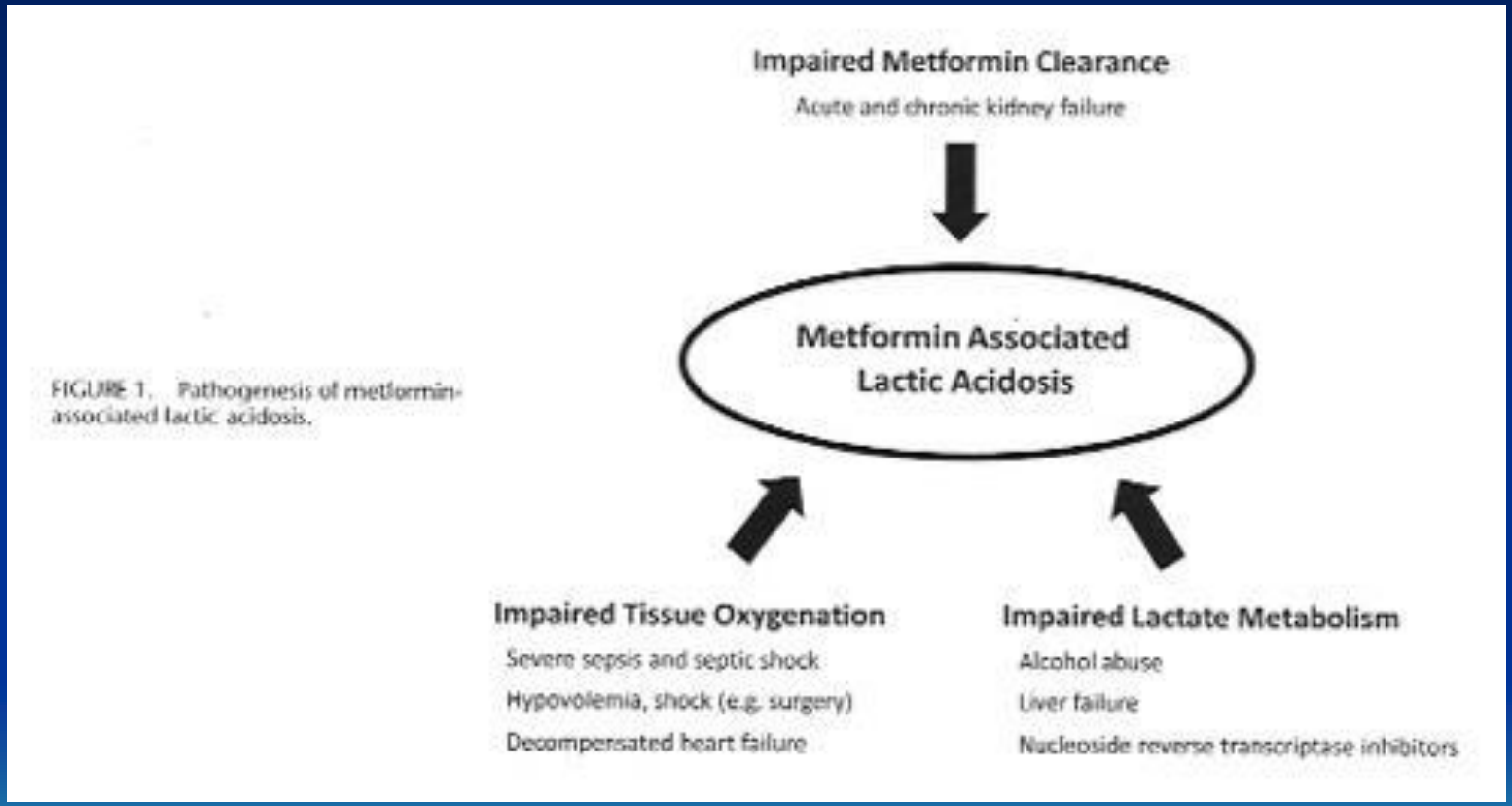

FIGURE 1. Pathogenesis of metformin-associated lactic acidosis.

AJMS, March 2015

Metformin Weirdness

- Toxicity depends on duration of metformin infusion
- Acute ingestion large doses
  - High initial serum drug levels, but only mild lactic acidosis.
- Intoxication over a few days
  - Lower serum drug level but extreme elevated lactic acidosis.

More Weirdness

- MALA is rare and is observed in association with an acutely worsening clinical condition.
- Interestingly, metformin concentration were, on average, three times higher in patients who survived.

Even More Weirdness

- In Severe Sepsis
  - Mortality lower in patients admitted to ER with severe LA and sepsis, when actively treated with Metformin.
  - Metformin
    - Has anti-inflammatory and anti-thrombotic effects
    - Can induce activation of AMP-activated protein kinase, resulting in increased use of ATP-generating pathways. Thus useful in times of increased stress.

World Dosing Guidelines

- UK:
  - Reduce dose GFR <45
  - Stop GFR < 30
- Canada & Canada:
  - No reduction until stop GFR < 30
- US:
  - Before: No use if Pcr 1.5 mg/dL males and 1.4 mg/dL females

New US Dosing Guidelines* - 1

- Contraindicated with eGFR <30 mL/min/1.73 m^2
- Starting with eGFR 30 to 45 mL/min/1.73 m^2 is not recommended
- If the eGFR falls below 45 mL/min/1.73 m^2 in a patient already taking metformin, the benefits and risks of continuing treatment should be assessed.

*FDA Drug Safety Communication April 20, 2016

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New US Dosing Guidelines* - 2

- Metformin should be not be administered for 48 hours after an iodinated contrast imaging procedure in patients with an eGFR <60 mL/min/1.73 m^2 or a history of liver disease, alcoholism, or heart failure, or in those receiving intra-arterial contrast, and the eGFR should be re-evaluated before treatment is restarted.

*FDA Drug Safety Communication April 20, 2016

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Daily Dose Adjustment

- Metformin is restricted to:
  - 500mg in GFR< 15 (Controversial)
  - 1000 mg with GFR < 30
  - 2000mg with GFR < 60
  - 3000 mg with GFR >60

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Conclusions

- Metformin is toxic to Mitochondria
- Metformin accumulates in decreased GFR
- Significant LA in Metformin patients vs non-Metformin patients debatable
- US guidelines may be too conservative
- Should other guidelines be adopted?

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