將軍澳醫院
Tseung Kwan O Hospital

Truth or myth?

Intensive care unit

Tseung Kwan O Hospital

Case

- F/64
- allergic to neosporin, chloramphenicol, hypromellose eye drops
- BH 146cm BW 60.9kg
- Past medical history
  - Post-RAI hypothyroidism
  - DM
  - Hyperlipidaemia
  - Old CVA with good recovery / CT brain: old left cerebral infarct
  - Psychosis FU psychiatry

Case

- Usual medications
  - Aspirin 80mg po daily
  - Pepcidine 20mg po BD
  - Diamicron 120mg po OM
  - Metformin 1000mg po BD
  - Thyroxine 100mcg po daily
  - Zestril 5mg po daily
  - Risperidone 3mg po nocte

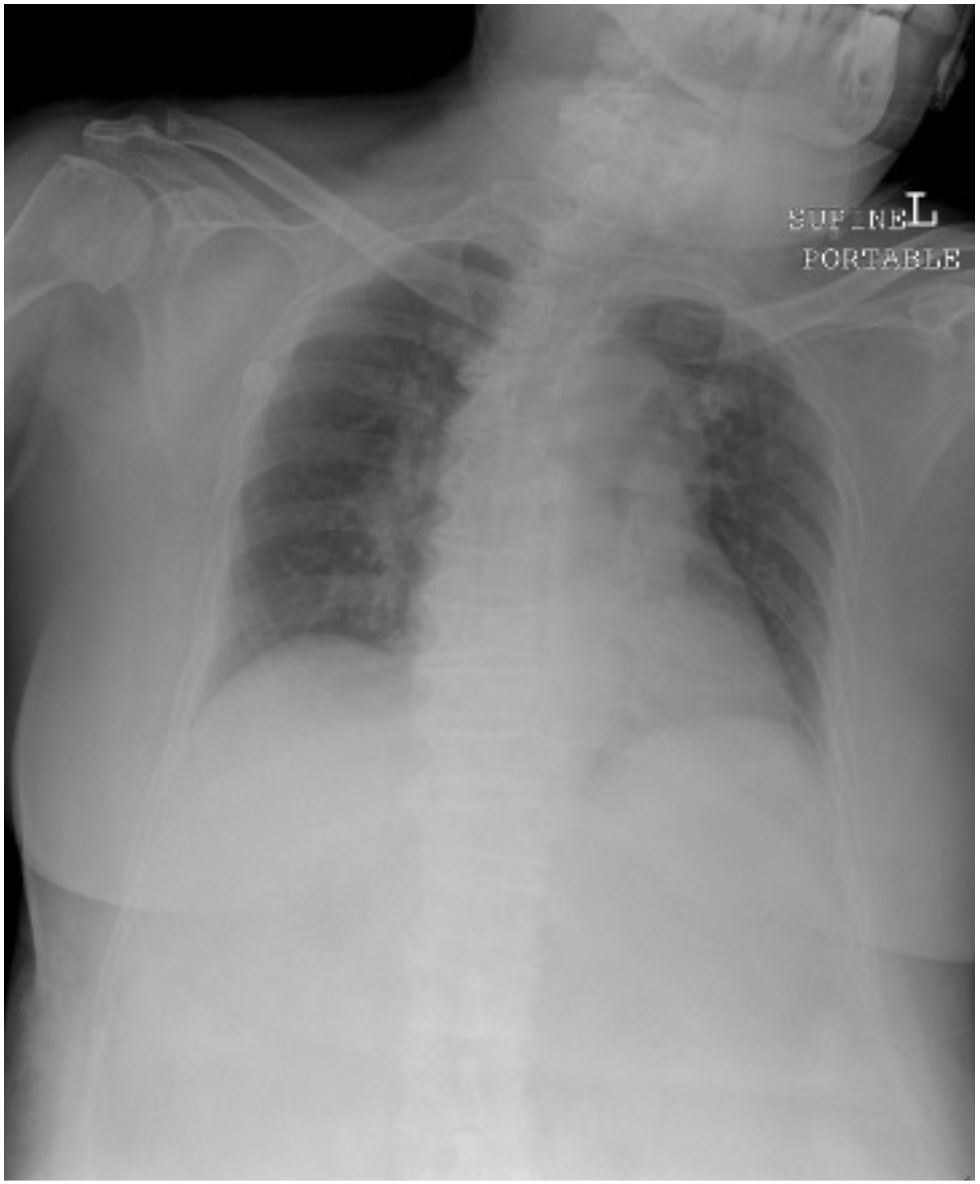
Case

- Admitted to medical ward for reduced appetite and poor oral intake for 3-4 days
- Vomiting of undigested food for several times
- Epigastric pain for several days
- Diarrhoea of watery loose stools before hospital admission
- No urinary symptoms
- Shortness of breath +, no chest pain, cough or sputum
- Dull looking, no fever, chills or rigors, no TOCC
- No herbs or over-the-counter medications taken
- No overdose of usual medications

Case

- Temp 33.2 GCS E4V4M6 BP 110/41 P 87/min RR 27/min
- SpO_2 100% on 2L/min O2 NC
- Chest: clear lung fields
- CVS: HS dual, no murmur
- Abdomen soft and non-tender
- CNS: no focal neurology
- H’stix 1.4 in AED
- ECG: atrial fibrillation, no acute ischaemic change

CXR



Case

- WBC 17.7 Hb 10.3 plt 184 INR 1.3
- RFT 135/8.3/28.1/874 <- RFT 137/4.5/10.1/108
- LFT normal amylase normal
- pH 6.90 pCO_2 2.0 pO_2 7.8 HCO_3 2.9 BE -28
- Lactate 13.21 (< 2.2)
- hstroponin < 14
- Zero urine output
- Transferred to ICU for close monitoring and renal support

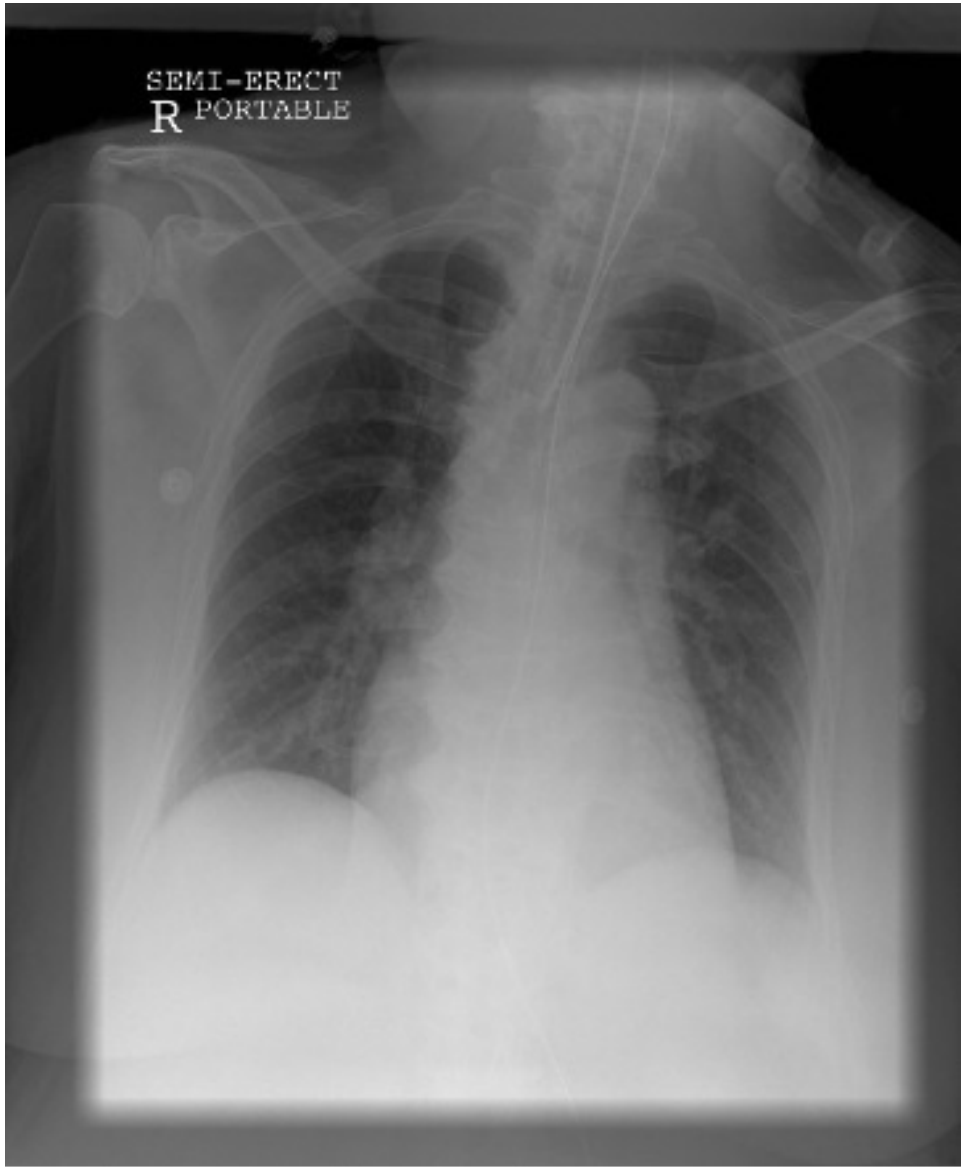
Case – D1 ICU

- Developed hypotension 66/34 after ICU admission
- Fluid resuscitation
- Dopamine and nor-adrenaline infusion started
- Amiodarone infusion for fast AF up to 150/min
- Empirical augmentin after septic work-up
- Started CVVHDF
- Vasopressin and hydrocortisone for refractory hypotension
- Antibiotics stepped up to meropenem

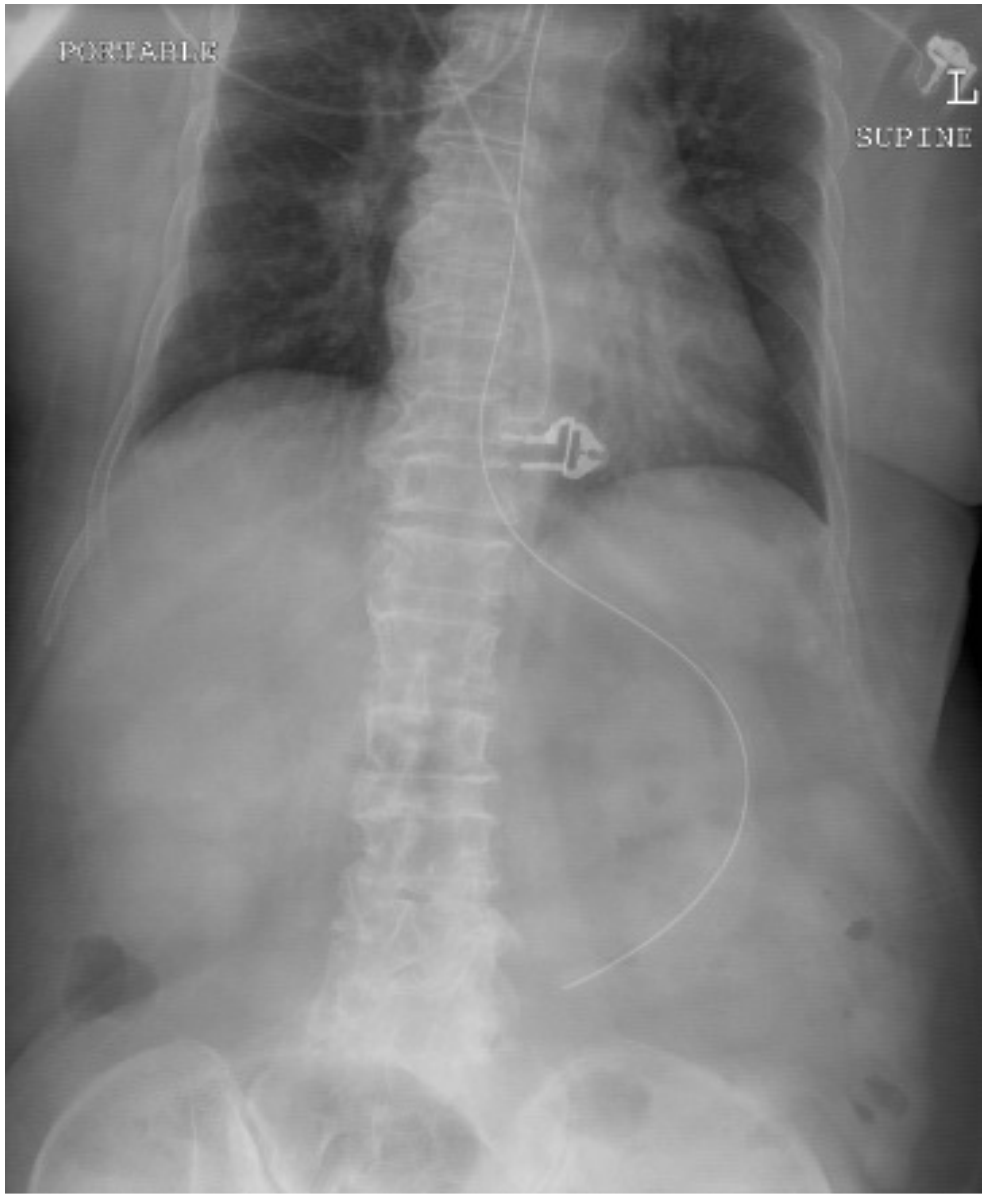
Case – D1 ICU

- GCS deteriorated E1V1M2
- Intubated to protect airway
- Highest dose of vasopressors required
  - Dopamine 200mg in 50ml NS at 30ml/hour (33 μg/kg/min)
  - Nor-adrenaline 8mg in 50ml D5 at 50ml/hour (2.2 μg/kg/min)
  - Vasopression 40 units in 50ml D5 at 3ml/hour (0.04 units/min)
- Bedside echo: LVEF 70%, no regional wall motion abnormality, no valvular lesion, no pericardial effusion

CXR



AXR



Case – D2 ICU

- WBC 15.5 Hb 7.5 plt 109
- RFT 133/4.1/12.5/341
- pH 7.50 pCO_2 4.0 pO_2 15.6 HCO_3 22.9
- CVVHDF stopped
- BP improved and vasopressin stopped
- Dose of dopamine and nor-adrenaline decreased
- Urine output regained

Case – D3 ICU

- RFT 136/2.9/11.2/296
- HCO3 20.7 pF ratio > 450
- Spontaneous diuresis
- GCS E3VTM6 -> extubated
- Doses of vasopressors keep decreasing
- Preliminary two blood C/ST results: no growth
- Preliminary urine C/ST: no growth, WBC and nitrite negative
- Meropenem stopped

Case – D4 ICU

- WBC 14.9 RFT 140/3.1/11.2/176 HCO3 21.0
- Dopamine infusion stopped
- Decreased dose of nor-adrenaline
- Tolerate oral feeding
- Hydrocortisone stopped
- Diamicron resumed

Case

- WBC normalised and RFT improved
- Electrolytes monitored and corrected
- Dose of nor-adrenaline is decreasing slowly
- Discharged from ICU on D7
- Formal blood and urine C/ST results: no growth

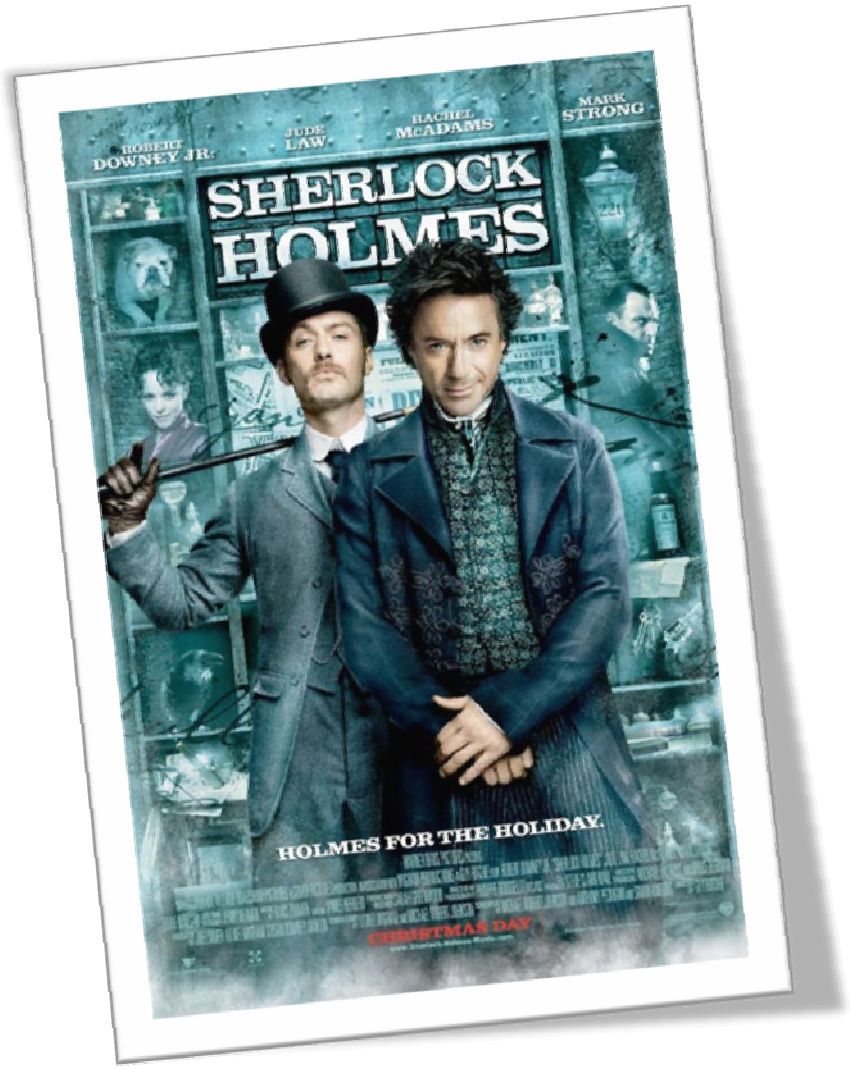
Cause of lactic acidosis?

- A. Sepsis
- B. Dehydration in DM patient
- C. Metformin
- D. A+B
- E. B+C
- F. A+B+C
- G. None of the above

Septic shock is unlikely in this patient…

- No definite source of sepsis was identified upon admission and during ICU stay
- Blood and urine C/ST were negative
- CXR was clear and pF ratio was good
- Clinical condition improved after 1 day of antibiotics
- Elevated WBC on admission could also be explained by other conditions such as stress and dehydration
- Shock could also present in lactic acidosis due to other causes apart from sepsis such as tissue hypoperfusion

Is metformin a ‘suspect’?



Metformin


COT
141


PRESCRIPTION ONLY MEDICINE
KEEP OUT OF REACH OF CHILDREN
Arrow - Metformin 500
Metformin Tablets
Each tablet contains metformin hydrochloride BP 500 mg
500 Tablets
PRESCRIPTION ONLY MEDICINE
KEEP OUT OF REACH OF CHILDREN
Arrow - Metformin 850
Metformin Tablets
Each tablet contains metformin hydrochloride BP 850 mg
250 Tablets


Metformin
500mg Tablets
84

Metformin

- Metformin is recommended as the drug of choice in patients with type 2 diabetes mellitus by
  - American Diabetic Association
  - European Association for the Study of Diabetes
  - Diabetes Australia Guideline Consortium
- Improves both peripheral and liver sensitivity to insulin
- Reduces gluconeogenesis in liver
- Increases insulin-stimulated uptake and utilization by peripheral tissue
- Lowers both fasting and post-prandial glucose concentration

Studies

- UK Prospective Diabetes Study (UKPDS) indicates metformin monotherapy lead to a reduction in diabetes-related endpoints and mortality, as compared to insulin, sulfonylurea therapy or diet alone
- Addition of metformin to insulin therapy significantly reduces macrovascular morbidity and mortality 40%
- ARR is 6.1% with a NNT 16 over a mean duration of 4.3 years
- Cochrane review found obese patients treated with metformin showed a significant benefit than sulfonylureas or insulin for any diabetes related outcome and total mortality

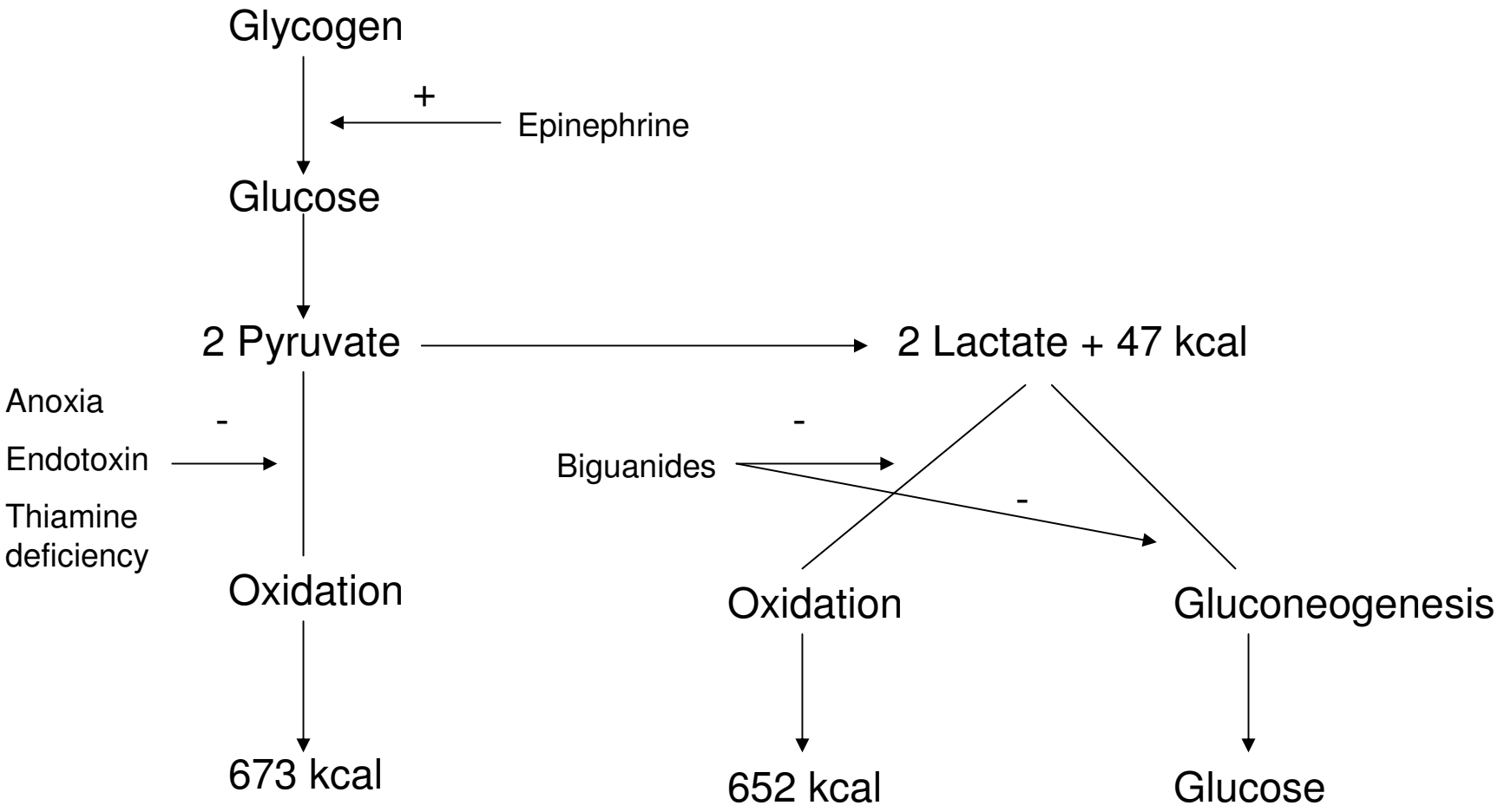
Side effects

- Gastrointestinal side effects occur on 20-30% of patients leading to discontinuation in <5% of patients
- Diarrhoea (10-53%)
- Nausea or vomiting (7-26%)
- Headache, agitation, dizziness and tiredness (6%)
- Megaloblastic anaemia, vitamin B12 deficiency (7%)
- Leukocytoclastic vasculitis (1%)
- Pnuemonitis (1%)
- ? Lactic acidosis (< 1%)

Lactic acidosis

- Accumulation of lactate (> 5 mmol/L) with decreased pH (pH < 7.20)
- Causes of lactate accumulation
  - Oxygen deprivation of cells in shock (e.g. hypovolaemic, cardiogenic and septic shock)
  - Endotoxaemia
  - Thiamine deficiency
  - Seizure (increase lactate production)
  - Liver insufficiency (reduce lactate clearance)
  - Epinephrine infusion
- Hyperlactatemia $\neq$ lactic acidosis

Glucose and lactate



Classification

- Cohen and Woods type A
  - Clinical evidence of poor tissue perfusion or oxygenation of blood (e.g. hypotension, cyanosis, cool and mottled extremities)
- Cohen and Woods type B
  - No clinical evidence of poor tissue perfusion or oxygenation
  - B1: presence of systemic diseases, such as acute renal and hepatic failure, diabetes and malignancy
  - B2: drugs and toxins
  - B3: inborn errors of metabolism

Lactic acidosis

- Mortality rate up to 50%
- Symptoms include malaise, myalgia, respiratory distress, drowsiness and abdominal pain
- Hypothermia, hypotension or bradyarrhythmia may occur
- Management would be supportive and removal of underlying cause

D-lactic acidosis

- Lactate produced by mammalian tissue is levo-isomer
- Dextro-isomer of lactate is produced by acid resistant bacteria (lactobacillis and streptococcus) in bowel
- Gain access to systemic circulation and cause metabolic acidosis, often combined with metabolic encephalopathy
- After extensive small bowel resection and after jejunoileal bypass for morbid obesity
- Not measured by standard laboratory assays

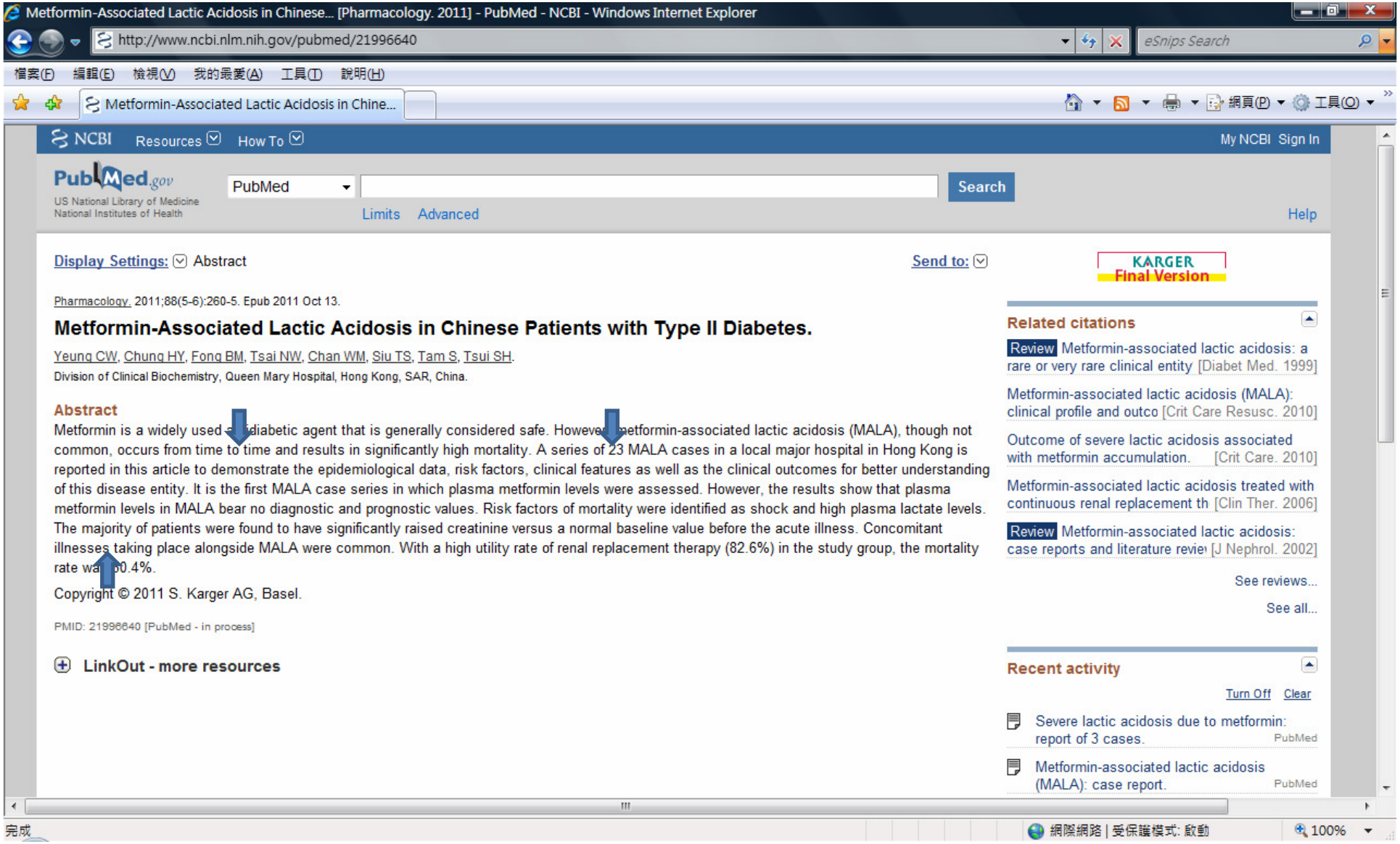
Biguanides and lactic acidosis

- Phenformin is the predecessor of metformin
  - decrease gluconeogenesis from alanine, pyruvate and lactate
  - inhibit hepatic uptake and oxidation of lactate
  - increase splanchinic production of lactate
- Some actions are due to affinity to mitochrondrial membrane, impairing the transport of reducing NADH
- Undergo partial biotransformation by liver
- Removed from market in 1977 due to unacceptably high incidence of associated lactic acidosis (about 1 case per 1000 patient-years)

Biguanides and lactic acidosis

- Metformin was marketed as Glucophage in early 1995
- Low affinity to mitochrondrial membrane
- Does not inhibit oxidative metabolism of lactate
- Tend to raise lactate by inhibiting gluconeogenesis
- Excreted unchanged in urine
- 3 cases of lactic acidosis per 100,000 patient-years according to manufacturer

- When we type ‘metformin associated lactic acidosis’ in www.pubmed.com....


Metformin-Associated Lactic Acidosis in Chinese... [Pharmacology. 2011] - PubMed - NCBI - Windows Internet Explorer
http://www.ncbi.nlm.nih.gov/pubmed/21996640
eSnips Search
檔案(F) 編輯(E) 檢視(V) 我的最愛(A) 工具(T) 說明(H)
Metformin-Associated Lactic Acidosis in Chine...
網頁(P) 工具(O)
NCBI Resources How To
My NCBI Sign In
PubMed.gov
US National Library of Medicine
National Institutes of Health
PubMed
Search
Limits Advanced
Help
Display Settings: Abstract
Send to:
KARGER
Final Version
Pharmacology. 2011;88(5-6):260-5. Epub 2011 Oct 13.
Metformin-Associated Lactic Acidosis in Chinese Patients with Type II Diabetes.
Yeung CW, Chung HY, Fong BM, Tsai NW, Chan WM, Siu TS, Tam S, Tsui SH.
Division of Clinical Biochemistry, Queen Mary Hospital, Hong Kong, SAR, China.
Abstract
Metformin is a widely used [illegible]diabetic agent that is generally considered safe. However, metformin-associated lactic acidosis (MALA), though not common, occurs from time to time and results in significantly high mortality. A series of 23 MALA cases in a local major hospital in Hong Kong is reported in this article to demonstrate the epidemiological data, risk factors, clinical features as well as the clinical outcomes for better understanding of this disease entity. It is the first MALA case series in which plasma metformin levels were assessed. However, the results show that plasma metformin levels in MALA bear no diagnostic and prognostic values. Risk factors of mortality were identified as shock and high plasma lactate levels. The majority of patients were found to have significantly raised creatinine versus a normal baseline value before the acute illness. Concomitant illnesses taking place alongside MALA were common. With a high utility rate of renal replacement therapy (82.6%) in the study group, the mortality rate wa[illegible]0.4%.
Copyright © 2011 S. Karger AG, Basel.
PMID: 21996640 [PubMed - in process]
LinkOut - more resources
Related citations
Review Metformin-associated lactic acidosis: a rare or very rare clinical entity [Diabet Med. 1999]
Metformin-associated lactic acidosis (MALA): clinical profile and outco [Crit Care Resusc. 2010]
Outcome of severe lactic acidosis associated with metformin accumulation. [Crit Care. 2010]
Metformin-associated lactic acidosis treated with continuous renal replacement th [Clin Ther. 2006]
Review Metformin-associated lactic acidosis: case reports and literature revie [J Nephrol. 2002]
See reviews...
See all...
Recent activity
Turn Off Clear
Severe lactic acidosis due to metformin: report of 3 cases. PubMed
Metformin-associated lactic acidosis (MALA): case report. PubMed
完成
網際網路 | 受保護模式: 啟動
100%

So…

- Are these cases of lactic acidosis really caused by metformin?
- Is it right to prescribe metformin to this patient in the beginning?
- Should we continue metformin for this patient after she recovers?

EDITORIAL

Metformin and Lactic Acidosis

Guilt by association?

Diabetes Care, volume 21, number 10, October 1998

Reviews/Commentaries/Position Statements

COMMENTARY

The Phantom of Lactic Acidosis due to Metformin in Patients With Diabetes

ROBERT I. MISBIN, MD

combinations with other antidiabetic

Diabetes Care, volume 27, Number 7, July 2004

Internal Medicine Journal **40** (2010) 342–346

ORIGINAL ARTICLE

Acidosis in the hospital setting: is metformin a common precipitant?

K. A. Scott,[1,2] J. H. Martin[1,3,4] and W. J. Inder[5,6]

Departments of [1]General Medicine and [5]Endocrinology, St Vincent's Hospital, [4]Department of Medicine, University of Melbourne, Melbourne, Victoria, [2]Department of Endocrinology, Royal Brisbane Hospital, [3]Department of Internal Medicine and Aged Care, Royal Brisbane and Women's Hospital and [4]Diamantina Institute, The University of Queensland, Brisbane, Queensland, Australia

- 101 episodes of acidosis identified
- Metabolic acidosis in 31%
- Mixed metabolic and respiratory acidosis in 40%
- 22 patients have type 2 DM and 5 of them has lactic acidosis
- Hepatic impairment, severe LV dysfunction and impaired renal function but not metformin use were associated with lactic acidosis

limitations

- Small sample size
- Retropective review
- Selection of inpatient cohort with high rates of co-morbidities and advanced age population

DM

Contra-indications to metformin therapy are largely disregarded

A. Holstein, D. Nahrwold, S. Hinze and E. -H. Egberts

- *Diabetic Medicine 16, 692-696*

- Cross-sectional analysis of 308 type 2 DM patients taking metformin admitted to hospital for acute illness or optimization of DM control
- No lactic acidosis was observed
- 19% of patients have chronic renal impairment
- 25% have heart failure, 6.5% have respiratory insufficiency and 1.3% have hepatic impairment

Epidemiology/Health Services/Psychosocial Research
ORIGINAL ARTICLE

Lactic Acidosis Rates in Type 2 Diabetes

- *Diabetes Care, volume 21, Number 10, October 1998*

- Measures the rate of lactic acidosis in type 2 DM patients for 12 full months in 1993, 1994 or both (before the era of metformin)
- 4 confirmed and 3 possible cases of lactic acidosis from > 41,000 patient-years
- Lactate level was not measured in possible cases, but they have high anion gap metabolic acidosis without evidence of ketoacidosis or uraemic acidosis

- 9.7 per 100,000 patient-years of lactic acidosis in metformin-naïve type 2 DM patients
- Rate increases up to 16.9 per 100,000 patient-years if possible cases are included

Clinical Care/Education/Nutrition
ORIGINAL ARTICLE

Comparative Outcomes Study of Metformin Intervention Versus Conventional Approach

The COSMIC Approach Study

- *Diabetes Care, volume 28, number 3, March 2005*

- Randomised, open-label, parallel group, 1-year trial in type 2 DM patients suboptimally controlled on diet or sulphonylurea
- Patients received metformin (n=7227) were compared with usual care (n=1505)
- Primary endpoints were serious adverse events, death and hopsitalisation

Table 1—*Characteristics of patients at baseline*

Initial	Metformin	Usual care
n	7,227	1,505
Mean age (years)	58.3 ± 12.9	58.8 ± 13.1
Age <65 years/≥65 years (%/%)	35/65	38/62
Male/female (%/%)	49.3/50.7	49.5/50.5
Race (%)		
White/Caucasian	78.0	76.2
African American	16.2	17.5
Asian	2.9	2.7
Other	2.8	3.6
Mean body weight (lbs)	204.0 ± 48.5	203.2 ± 48.2
Mean body weight (kg)	92.5 ± 22.0	92.2 ± 21.9
Mean diabetes duration (years)	4.9 ± 5.9	4.7 ± 6.0
Previous therapy (%)		
Diet	41.0	35.1
Diet + sulfonylurea	58.5	64.3
Not reported	0.5	0.5

Data are means ± SD. Information on age was not captured for three patients (two in the metformin group and one in the usual care group); these patients are not included in the percentages of patients stratified by age.

Table 2—*Overall incidence of SAEs and summary of SAEs by system organ class* (Medical Dictionary for Regulatory Affairs; *SAEs in individual organ classes ≥1.0% in either group before stratification for age) in the metformin or usual care treatment groups: number and percent of patients*

	All patients		Age <65 years		Age ≥65 years	
	Metformin	Usual care	Metformin	Usual care	Metformin	Usual care
n	7,227	1,505	4,710	935	2,515	569
Any SAE	747 (10.3)	166 (11.0)	375 (8.0)	73 (7.8)	371 (14.8)	93 (16.3)
Cardiac disorders	237 (3.3)	49 (3.3)	96 (2.0)	17 (1.8)	141 (5.6)	32 (5.6)
Gastrointestinal disorders	88 (1.2)	18 (1.2)	44 (0.9)	4 (0.4)	44 (1.7)	14 (2.5)
General disorders*	158 (2.2)	39 (2.6)	60 (1.3)	19 (2.0)	98 (3.9)	20 (3.5)
Infections and infestations	121 (1.7)	32 (2.1)	49 (1.0)	10 (1.1)	72 (2.9)	22 (3.9)
Metabolism and nutritional disorders	70 (1.0)	11 (0.7)	35 (0.7)	6 (0.6)	34 (1.4)	5 (0.9)
Neoplasms†	92 (1.3)	20 (1.3)	41 (0.9)	6 (0.6)	51 (2.0)	14 (2.5)
Vascular disorders	92 (1.3)	36 (2.4)	40 (0.8)	16 (1.7)	52 (2.1)	20 (3.5)

Data are *n* (%). *Includes administration site conditions; †benign, malignant, and unspecified (including cysts and polyps). Information on age was not captured for three patients (two in the metformin group and one in the usual care group); data for these patients are included in the 'All patients' section but not in the sections stratified for age at baseline.

- Similar serious adverse events between groups
- No lactic acidosis was observed
- No significant difference between mortality and hospitalization

Table 3—*Mortality and hospitalizations*

	Metformin (n = 7,227)	Usual care (n = 1,505)	P
All-cause mortality			
All patients (n = 7,227)	1.1 (0.9–1.4)	1.3 (0.8–2.0)	0.596
Patients <65 years (n = 5,645)	0.4 (0.3–0.7)	0.7 (0.3–1.5)	0.21
Patients ≥65 years (n = 3,084)	2.4 (1.8–3.1)	2.1 (1.1–3.7)	0.878
Mortality from lactic acidosis*			
All patients (n = 7,227)	0 (0.00–0.05)	0 (0.00–0.24)	—
All-cause hospitalizations			
All patients (n = 7,227)	9.4 (8.8–10.1)	10.4 (8.9–12.1)	0.229
Patients <65 years (n = 5,645)	7.3 (6.6–8.1)	7.4 (5.8–9.3)	0.945
Patients ≥65 years (n = 3,084)	13.3 (12.0–14.7)	15.5 (12.6–18.7)	0.178
Hospitalizations for lactic acidosis*			
All patients (n = 7,227)	0 (0.00–0.05)	0 (0.00–0.24)	—
Hospitalizations for other metabolic causes			
All patients (n = 7,227)	0.9 (0.7–1.2)	0.9 (0.5–1.6)	1.000
Patients <65 years (n = 5,645)	0.7 (0.5–1.0)	0.7 (0.3–1.5)	0.835
Patients ≥65 years (n = 3,084)	1.3 (0.9–1.8)	1.2 (0.5–2.5)	1.000

Data are percent of patients (95% CI). *Data on mortality or hospitalizations due to lactic acidosis are given for all patients only, as no events due to lactic acidosis were reported. Information on age was not captured for three patients (two in the metformin group and one in the usual care group); data for these patients are included in the 'All patients' section but not in the sections stratified for age at baseline. For numbers of patients aged <65 years or ≥65 years, see Table 2.

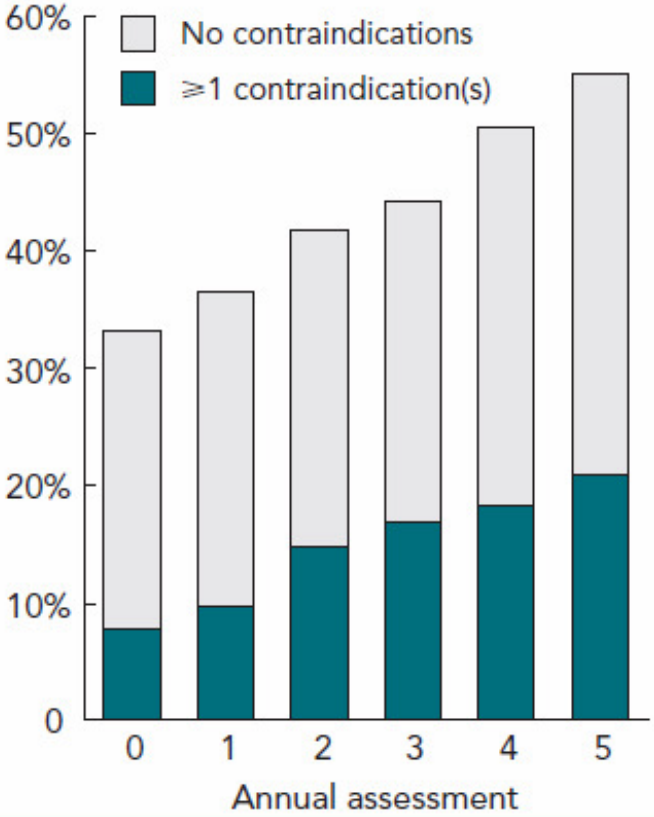
Metformin and lactic acidosis in an Australian community setting: the Fremantle Diabetes Study

Niklaus Kamber, Wendy A Davis, David G Bruce and Timothy M E Davis

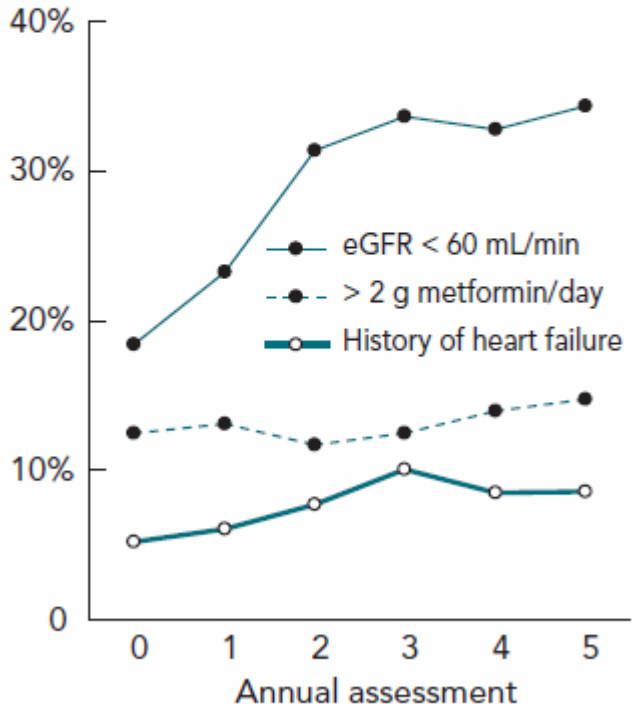
- *Med J Australia 2008; 188: 446 – 449*

- Study the incidence of lactic acidosis in 1279 community patients in Western Australia with type 2 DM, with reference to metformin
- 33.3% was treated with metformin and 23.1% had contraindication when study started in 1996
- 55.1% was treated with metformin and 38.0% had contraindication after follow up for 5 years

1 Percentages of patients in the Fremantle Diabetes Study taking metformin at each annual review, and percentages with and without contraindications to metformin use



2 Percentages of patients in the Fremantle Diabetes Study, of those prescribed metformin, with renal failure, a history of heart failure, or taking a high dosage of metformin, at each annual review



eGFR = estimated glomerular filtration rate. ◆

3 Patients from the Fremantle Diabetes Study with confirmed lactic acidosis

Patient no.	Age (years)	Sex	Metformin (g/day)	Arterial pH	Plasma lactate (mmol/L)	Serum bicarbonate (mmol/L)	Serum creatinine (μmol/L)	Other conditions	Outcome
1	86	F	Yes (1.0)	7.15	9.1	23	164	Myocardial infarction, acute renal failure, type 2 respiratory failure	Discharged
2	71	F	Yes (2.0)	6.79	13.8	5	79	Cardiogenic shock, thromboembolic disease	Died
3	70	F	Yes*	6.81	17.5	3	940	Chronic renal failure	Discharged
4	65	F	No	7.34	9.5	Unknown	Unknown	End-stage renal failure, septic shock	Died
5	48	M	No	7.08	10.9	14	227	Myocardial infarction, acute renal failure	Discharged

*Dosage unknown.

- 3 lactic acidosis per 5228 patient-years in metformin group and 2 cases per 7238 patient-years in non-metformin group after 10 years' follow up
- Weakness was small total patient-years of follow-up

Clinical Care/Education/Nutrition/Psychosocial Research
ORIGINAL ARTICLE

Metformin, Sulfonylureas, or Other Antidiabetes Drugs and the Risk of Lactic Acidosis or Hypoglycemia

A nested case-control analysis

- *Diabetes Care, volume 31, number 11, November 2008*

- 6 cases of lactic acidosis identified among the study population of 50,047 type 2 DM patients
- Crude incidence of lactic acidosis was 3.3/100,000 patient-years among metformin users and 4.8/100,000 patient-years among sulfonylureas users
- Risk factors for lactic acidosis identified in all case subjects

Clinical Endocrinology (2011) **74**, 191–196 doi: 10.1111/j.1365-2265.2010.03891.x

ORIGINAL ARTICLE

Diabetes, metformin and lactic acidosis

T. Scale and J. N. Harvey

Wrexham Academic Unit, Centre for Endocrinology and Diabetes, Wales College of Medicine, Cardiff University, Wrexham, UK

- Retrospective analysis of all lactic acidosis in a hospital in UK
- Classified as patients with and without DM, those taking metformin or not
- Information on numbers of DM patients and those taking metformin in local population was provided by two large local general practices

	DM with metformin	DM without metformin	Non-diabetic
Annual incidence rate per 1000 patients	1.2	1.8	0.1

Table 2. All the identified cases of lactic acidosis (using criteria of lactate >5 mM and pH ≤ 7·2) classified into Cohen and Woods class A and B. The distribution of factors known to predispose to lactic acidosis between these two classes is shown

Cohen and Woods classification			
	A	B	P
N	76	73	
Male (%)	43 (57)	35 (48)	0·29
Deceased (%)	47 (62)	34 (47)	0·061
Age (years)	67·3 ± 1·9	62·5 ± 2·5	0·044
H^+ (10^{-9} M)	88·5 ± 3·2	85·7 ± 2·9	0·72
Lactate (mM)	10·2 ± 0·4	11·6 ± 0·6	0·004
All diabetes (%)	19 (25)	35 (48)	0·004
Type 2 diabetes (%)	19 (25)	29 (40)	0·054
Metformin (%)	10 (13)	18 (25)	0·07
Acute renal failure (%)	34 (45)	39 (53)	0·29
Chronic renal failure (%)	11(14)	12 (16)	0·74
eGFR (ml/min)	42·5 ± 3·2	39·8 ± 3·4	0·62
Ischaemic heart disease (%)	43 (57)	24 (33)	0·004
Sepsis (%)	22 (29)	34 (47)	0·4
Seizure (%)	1 (1)	18 (25)	<0·001
Alcoholism (%)	6 (8)	14 (19)	0·043
Hypothermia (%)	6 (8)	4 (5)	0·56
Cancer (%)	9 (12)	10 (14)	0·73
Liver disease (%)	6 (8)	9 (12)	0·37

Data are number of cases (% of the total in that class) or mean ± SEM. Means are compared by *t*-test. Frequency of parameters in the two classes is compared by chi-square test.

Table 3. Numbers of patients with the various risk factors for lactic acidosis in patients with diabetes on and not on metformin and patients without diabetes. Cohen and Woods class A (tissue hypoxia because of cardiorespiratory disease) and B (no significant acute cardiorespiratory disturbance) are shown

	Cohen and Woods classification Class A			Cohen and Woods classification Class B			
	Patients with type 2 diabetes			Patients with type 2 diabetes			
	On metformin	Not on metformin	No diabetes	On metformin	Not on metformin	No diabetes	ANOVA Type B patients
N	10	9	57	18	11	38	
Male	3	8	32	9	4	19	
Deceased	7	5	35	10	5	19	
Age (years)	60·9 ± 3·4	74·2 ± 2·4	67·3 ± 2·4	71·4 ± 3·0	72·1 ± 5·7	60·4 ± 3·3*	$F = 3·2$, $P = 0·049$
H^+ (10^{-9} M)	97·1 ± 10·8	105·1 ± 10·6	84·4 ± 3·3	93 ± 8·2	87·6 ± 8·1	81·4 ± 3·2	$F = 1·3$, $P = 0·28$
Base excess	−14·3 ± 3·0	−18·3 ± 1·4	−14·1 ± 0·8	−20·3 ± 1·7***	−10·1 ± 1·6**	−16·4 ± 0·8*	$F = 11·0$, $P < 0·001$
Lactate (mM)	10·7 ± 1·3	11·6 ± 1·1	9·9 ± 0·5	10·6 ± 1·1	8·4 ± 0·8**	13·6 ± 0·8*	$F = 6·9$, $P = 0·002$
Acute renal failure	6	2	26	15	3	16	
Chronic renal failure	1	2	8	3	4	5	
eGFR (ml/min)	35·7 ± 10·8	37·7 ± 5·8	44·6 ± 3·7	20·4 ± 3·7**	42·4 ± 5·9	48·3 ± 5·2	$F = 6·6$, $P = 0·003$
Ischaemic heart dis	8	9	24	8	6	9	
Sepsis	4	4	23	8	6	19	
Seizure	0	0	1	1	3	13	
Alcoholism	0	0	6	2	0	10	
Hypothermia	0	1	5	1	1	2	
Cancer	0	2	7	5	1	4	
Liver disease	0	0	4	0	1	8	

Data are number of cases or mean ± SEM. ANOVA showed no significant differences in Class A, so the ANOVA results shown refer to Class B only. Post hoc tests (Tukey's LSD) are given as *$P < 0·05$ *vs* metformin-treated group, **$P \leq 0·002$ *vs* nondiabetic group, ***$P < 0·001$ *vs* patients with diabetes not on metformin.

Table 5 Numbers of patients with fatal outcome according to presence of risk factors for lactic acidosis

	All	Dead *n* (%)	Alive	*P*
Total cohort (*n*)	149	81 (54)	68	
Age (years)	64·9 ± 1·6	70·9 ± 1·7	57·8 ± 2·5	0·01
Male	78	37 (47)	41	0·075
Female	71	44 (62)	27	
Cohen and Woods				
Class A	76	47 (62)	29	0·061
Class B	73	34 (47)	39	
Lactate (mM)	10·9 ± 0·4	10·6 ± 0·4	11·3 ± 0·6	0·10
H^+ (10^{-9} M)	87·1 ± 2·2	86·3 ± 2·8	88·2 ± 3·4	0·10
Diabetes	54	27 (50)	27	0·42
Metformin	28	17 (61)	11	0·45
eGFR (ml/min)	41·2 ± 2·3	33·5 ± 2·4	50·4 ± 3·9	0·001
Acute renal failure	73	46 (63)	27	0·038
Ischaemic heart dis	65	39 (60)	26	0·22
Sepsis	65	44 (68)	21	0·005
Seizure	19	0 (0)	19	<0·001
Alcoholism	20	10 (50)	10	0·67
Cancer	19	12 (63)	7	0·41
Hypothermia	10	7 (70)	3	0·30
Liver disease	15	10 (67)	5	0·31

Data are number of cases or mean ± SEM. Means are compared by *t*-test. For the parameters given as counts (numbers of patients), a chi-square test was used to assess the association between presence or absence of the clinical parameter and outcome.

- DM is proposed to be associated with lactic acidosis rather than metformin in this study

Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus (Review)

Salpeter SR, Greyber E, Pasternak GA, Salpeter EE

THE COCHRANE COLLABORATION®

- 347 studies were analysed
  - 209 were prospective comparative trials
  - 125 were prospective cohort studies
  - 13 were retrospective cohort studies
- 19 trials were specifically designed to assess the incidence of lactic acidosis
- Side effects or adverse events were described in almost all trials
- Of the 334 prospective studies, 53% allowed inclusion of renal insufficiency and 97% included at least one of the contraindications

- Upper limit of true incidence of lactic acidosis
  - 4.3 / 100,000 patient-years in metformin group
  - 5.4/ 100,000 patient-years in non-metformin group
- *Authors' conclusion: No evidence from prospective comparative trials or from observational cohort studies that metformin treatment increases the incidence of lactic acidosis compared with other anti-hyperglycaemic treatments*
- Large prospective, comparative trials are necessary in patients with type 2 DM who have condition that are presently contraindicated for its use

DM as risk factor for lactic acidosis

- Micro- or macrovascular disease in DM may cause relative tissue hypoxia leading to anaerobic glycolysis
- Type 2 DM do have mild hyperlactataemia under basal condition attributing to a defect in pyruvate oxidation
- DM patients were more likely to have sepsis, dehydration or acute cardiac event which perpetuate the chronic hypoxia condition
- Raised lactate in DKA was partly due to inhibitory effect of ketones on hepatic lactate uptake

DM as risk factor for lactic acidosis

- Possible precipitating factors for lactic acidosis in DM
  - Acute renal failure
  - Acute liver failure
  - Sepsis
  - Dehydration
  - Acute cardiac events (acute coronary syndrome, congestive heart failure)
  - Acute pulmonary disease (asthma, acute excerbation of COPD)
- Continuation of metformin in acute illness theoretically has the tendency to perpetuate hyperlactatemia

More lenient guidelines for metformin use?

- No definite causal relationship between metformin and lactic acidosis is established when being taken in usual therapeutic dose, even including those with traditional contraindications
- Judicious use of metformin improved diabetic-related morbidity and mortality

Commentary

Commentaire

Metformin's contraindications should be contraindicated

- *CMAJ, Aug 30, 2005: 173(5)*

Key points

- The most common contraindications to metformin use in people with type 2 diabetes are renal insufficiency, congestive heart failure and advanced age (≥ 80 years).
- Results from most major studies and a recent meta-analysis suggest that metformin use does not increase the risk of lactic acidosis among patients with type 2 diabetes, including those with these contraindications.
- In the case reports of lactic acidosis in people with contraindications who took metformin, it is difficult to determine the degree to which the drug was responsible.
- Even in patients with contraindications, the benefits of metformin use clearly outweigh any potential risks.

A. Holstein · M. Stumvoll

Contraindications can damage your health—is metformin a case in point?

- *Diabetologia (2005) 48: 2454 – 2459*

Table 1 Current contraindications and precautions to the use of metformin

Contraindication	Manufacturers (Package insert), 2005 [5]	German Diabetes Association, 2003 [8]	British National Formulary, 2005 [6]	UK national clinical guidelines, 2002 [7]	Howlett and Bailey, 1999 [9]
Impaired renal function	Creatinine clearance <60 ml/min	Serum creatinine >107 µmol/l	Serum creatinine >133 µmol/l	Serum creatinine >133 µmol/l	Creatinine clearance <90 ml/min
Heart failure	yes	yes	yes	not stated	yes
(Advanced) cardiovascular disease	not stated	not stated	not stated	not stated	yes
Respiratory failure	yes	yes	yes	not stated	yes
Severe liver disorders	yes	yes	yes	not stated	yes
Tissue hypoxia	yes	yes	yes	not stated	yes
Acute and chronic alcohol abuse	yes	yes	not stated	not stated	yes
Advanced age	not stated	yes	not stated	not stated	not stated
Before i.v. contrast medium administration	yes	yes	yes	not stated	not stated
Perioperatively	not stated	yes	yes	not stated	not stated
Hypocaloric diets (<1,000 kcal)	not stated	yes	not stated	not stated	not stated
Wasting diseases	not stated	yes	not stated	not stated	not stated
Pregnancy, lactation	yes	not stated	yes	not stated	yes
Diabetic ketoacidosis, diabetic precoma	yes	not stated	yes	not stated	yes

Table 2 Adherence to metformin contraindications as shown by population-based studies and retrospective samples

Authors/ Time period	Number of patients	Country/ Region	Frequency of all contraindications and risks (%)	Frequency of renal impairment (%)	Frequency of liver disorders (%)	Frequency of heart failure (%)	Frequency of CHD including myocardial infarction (%)	Number of cases of lactic acidosis
Sulkin et al. [10] 3 months	89	England Southampton	54	2	2	2	22	0
Holstein et al. [11] 3.5 years	308	Germany Lippe	74	19	1.3	25	51	0
Emslie-Smith et al. [12] 3 years	1,847	Scotland Tayside	24.5	4.8	2.8	25.2	3.5	1
Horlen et al. [13] 9 months	100	USA North Carolina	22	5	Not stated	14	Not stated	0
Calabrese et al. [14] 6 months	204	USA Pittsburgh	62	12	Not stated	Not stated	Not stated	0
Kennedy and Herman [36]	4,838	USA	Not stated	4.5	Not stated	Not stated	Not stated	Not stated
Rakovac et al. [37] 5 years	4,401	Austria	18.9	3.1	Not stated	13.6	Not stated	Not stated

- Proposed advanced age per se, mild renal impairment and compensated heart failure can no longer be upheld as contraindications for metformin
- Estimated GFR as low as 40ml/min may be acceptable to continue metformin
- Stable heart failure of NYHA stages I and II that is effectively controlled by diuretics and ACEI should no longer be contraindication
- Safe to withdraw metformin the evening before IV contrast media with normal renal function in view of low lipophilicity and short plasma half-life of metformin

Int Urol Nephrol (2008) 40:411–417
DOI 10.1007/s11255-008-9371-6

REVIEW

Metformin: effective and safe in renal disease?

William Guy Herrington · Jeremy B. Levy

- Continue meformin in stage 1-2 CKD, GFR 60-90 ml/min
- Reduce starting and maximal dose by half in stage 3 CKD, GFR 30-60 ml/min
- When GFR < 30ml/min, risk and benefit of metformin should be balanced
- Also advised to stop metformin in acute illness predisposing to hypoxia or acute renal failure

NEPHROLOGY

Nephrology **15** (2010) 412–418

Review Article

Review: Metformin: Potential benefits and use in chronic kidney disease

HELEN L PILMORE

Department of Renal Medicine, Auckland City Hospital and University of Auckland, Auckland, New Zealand

- Metformin use in patients with stage 1 or 2 chronic kidney disease and after renal transplantation would result in possible cardio-vascular and survival benefits

SUMMARY AT A GLANCE

While metformin is an old drug, recent data on its mechanism of action have led to a review of the recommendations for use in CKD. Additionally, there is interest in ANZ to trial metformin in the post-transplant context. A succinct overview of the current state of clinical knowledge regarding the use of this agent is provided.

Guidelines for the management of chronic kidney disease

Adeera Levin MD, Brenda Hemmelgarn MD PhD, Bruce Culleton MD MSc, Sheldon Tobe MD, Philip McFarlane MD PhD, Marcel Ruzicka MD PhD, Kevin Burns MD, Braden Manns MD MSc, Colin White MD, Francoise Madore MD MSc, Louise Moist MD MSc, Scott Klarenbach MD MSc, Brendan Barrett MD MSc, Robert Foley MD MSc, Kailash Jindal MD, Peter Senior MBBS PhD, Neesh Pannu MD MSc, Sabin Shurraw MD, Ayub Akbari MD, Adam Cohn MD, Martina Reslerova MD PhD, Vinay Deved MD, David Mendelssohn MD, Gihad Nesrallah MD, Joanne Kappel MD, Marcello Tonelli MD SM, for the Canadian Society of Nephrology

- *CMAJ, November 18, 2008, 179 (11)*

Use of metformin in type 2 diabetes mellitus

- Metformin is recommended for most patients with type 2 diabetes with stage 1 or 2 chronic kidney disease who have stable renal function that has been unchanged over the past 3 months (grade A).
- Metformin may be continued in patients with stable stage 3 chronic kidney disease (grade B).
- **Clinical practice recommendation:** Metformin should be stopped if there are acute changes in renal function or during periods of illnesses that could precipitate such changes (e.g., gastrointestinal upset or dehydration) or cause hypoxia (e.g., cardiac or respiratory failure). Particular care should be taken for patients also taking ACE inhibitors, angiotensin-receptor blockers, nonsteroidal anti-inflammatory drugs or diuretics, or after intravenous contrast administration because the risk of acute renal failure, and thus accumulation of lactic acid, is greatest for these patients.

nephron Clinical Practice

Nephron Clin Pract 2011;118:c380–c383
DOI: 10.1159/000323739

Published online: February 16, 2011

Metformin: The Safest Hypoglycaemic Agent in Chronic Kidney Disease?

Helen J. Nye[a] William G. Herrington[b]

[a]North Bristol NHS Trust, Bristol, and [b]Oxford Kidney Unit, Churchill Hospital, Oxford Radcliffe Hospitals NHS Trust, Oxford, UK

- Metformin is always avoided in patients with acute deterioration of renal function and in whom oxygenation and tissue perfusion is severely compromised
- In type 2 DM patients with stable chronic renal disease, clinicians should not prematurely or unnecessarily withdrawing metformin treatment

REVIEW

Use of Metformin in the Setting of Mild-to-Moderate Renal Insufficiency

- *Diabetes Care, volume 24, June 2011*

Table 1—*Proposed recommendations for use of metformin based on eGFR*

eGFR level (mL/min per 1.73 m^2)	Action
≥60	No renal contraindication to metformin
	Monitor renal function annually
<60 and ≥45	Continue use
	Increase monitoring of renal function (every 3–6 months)
<45 and ≥30	Prescribe metformin with caution
	Use lower dose (e.g., 50%, or half-maximal dose)
	Closely monitor renal function (every 3 months)
	Do not start new patients on metformin
<30	Stop metformin

Additional caution is required in patients at risk for acute kidney injury or with anticipated significant fluctuations in renal status, based on previous history, other comorbidities, or potentially interacting medications.

- Such proposals, being consistent with well-respected national guidelines committee, should be reviewed by professional medical organizations in the US, such as the American Diabetes Association
- If a consensus emerges, perhaps the FDA might reconsider the current metformin prescribing guidelines

Diabetologia (2010) 53:2546–2553
DOI 10.1007/s00125-010-1906-6

ARTICLE

Metformin treatment is associated with a low risk of mortality in diabetic patients with heart failure: a retrospective nationwide cohort study

C. Andersson · J. B. Olesen · P. R. Hansen · P. Weeke · M. L. Norgaard · C. H. Jørgensen · T. Lange · S. Z. Abildstrøm · T. K. Schramm · A. Vaag · L. Køber · C. Torp-Pedersen · G. H. Gislason

- 10,920 DM patients aged > 30 years hospitalized for the first time of heart failure were assigned mono-, bi- or triple therapy
- Over median observation time of 844 days, treatment with metformin is associated with a low risk of mortality compared with treatment with sulfonylurea or insulin
- No lactic acidosis were identified over the study period

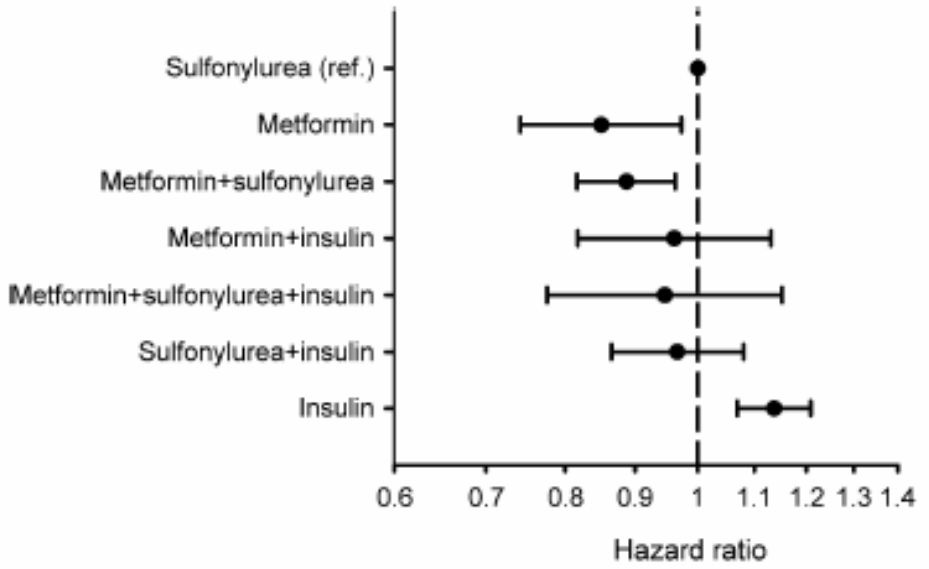


Fig. 1 Results from multivariable Cox analysis of all-cause mortality according to baseline treatment modality. Ref., reference

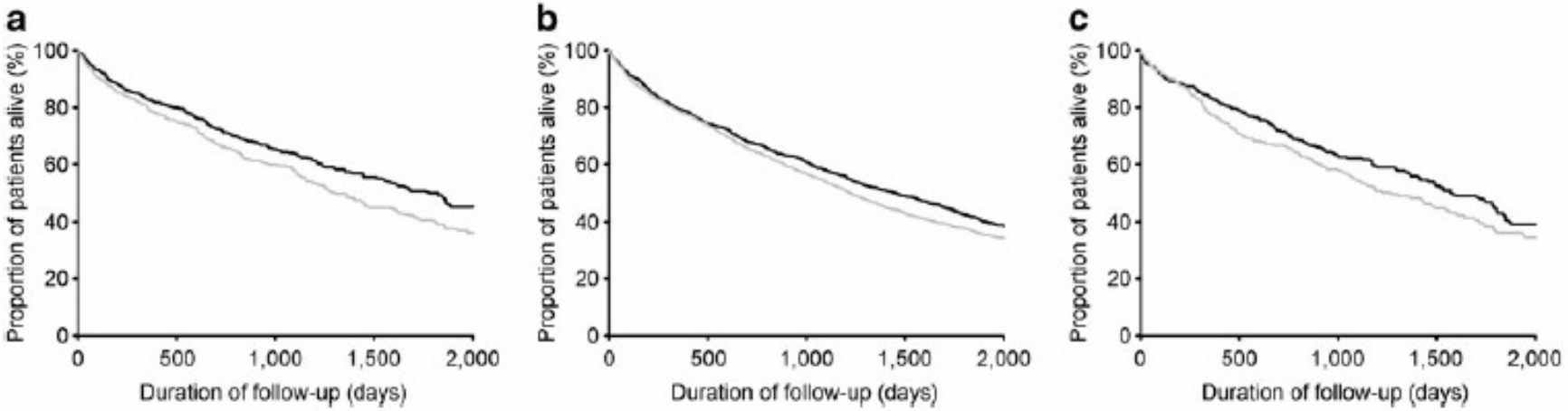


Fig. 3 Kaplan–Meier mortality curves for subgroups of patients treated with (**a**) metformin monotherapy (black line) vs sulfonylurea monotherapy (grey line); (**b**) metformin + sulfonylurea (black line) vs sulfonylurea monotherapy (grey line); and (**c**) metformin + insulin (black line) vs insulin monotherapy (grey line). All subgroups were matched on baseline characteristics. Logrank $p<0.05$ for all three analyses

Contents lists available at SciVerse ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

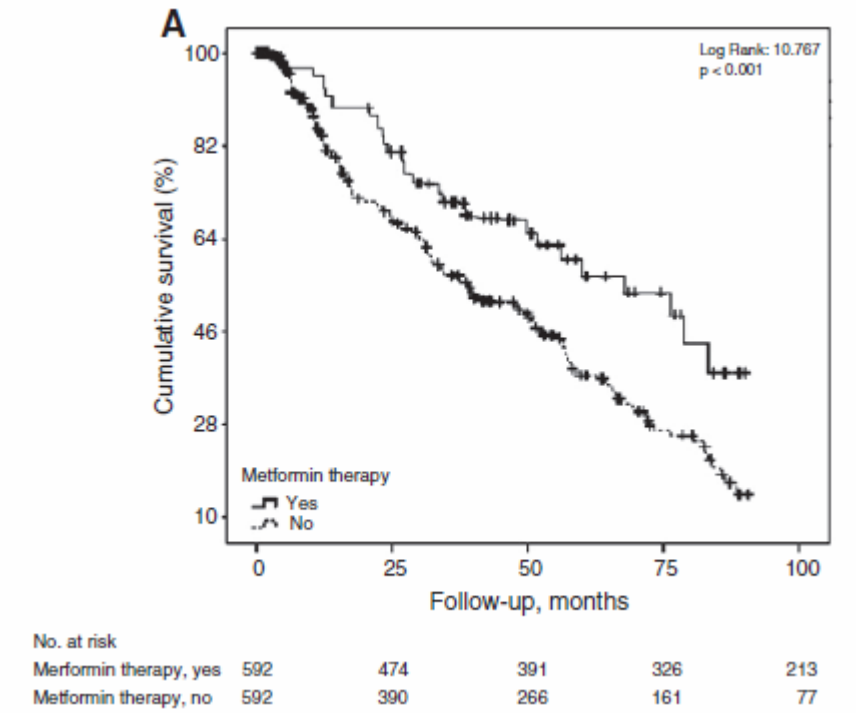
Metformin therapy and prognosis of patients with heart failure and new-onset diabetes mellitus. A propensity-matched study in the community

Sotero P. Romero, Jose L. Andrey, Antonio Garcia-Egido, Miguel A. Escobar, Virginia Perez, Ramón Corzo, Gloria J. Garcia-Domiguez, Francisco Gomez *

Department of Medicine, Hospital Universitario Puerto Real, Cadiz, Spain

- Prospective study of 1,519 patients with newly-diagnosed DM and heart failure during 9 years
- 39% patients did not receive metformin and they were matched with 592 patients taking metformin using propensity-score
- Metformin group had decreased mortality, mainly due to reduced cardiovascular mortality, and with a lower hospitalization rate

- No association with an improved prognosis with a mean HbA1c <= 7.0%
- No case of lactic acidosis was observed



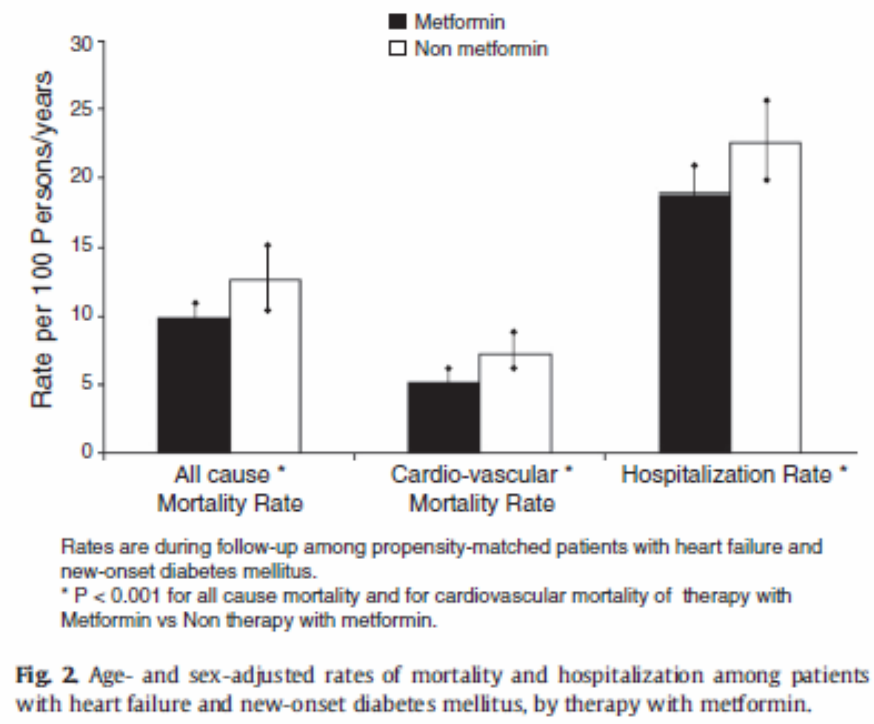
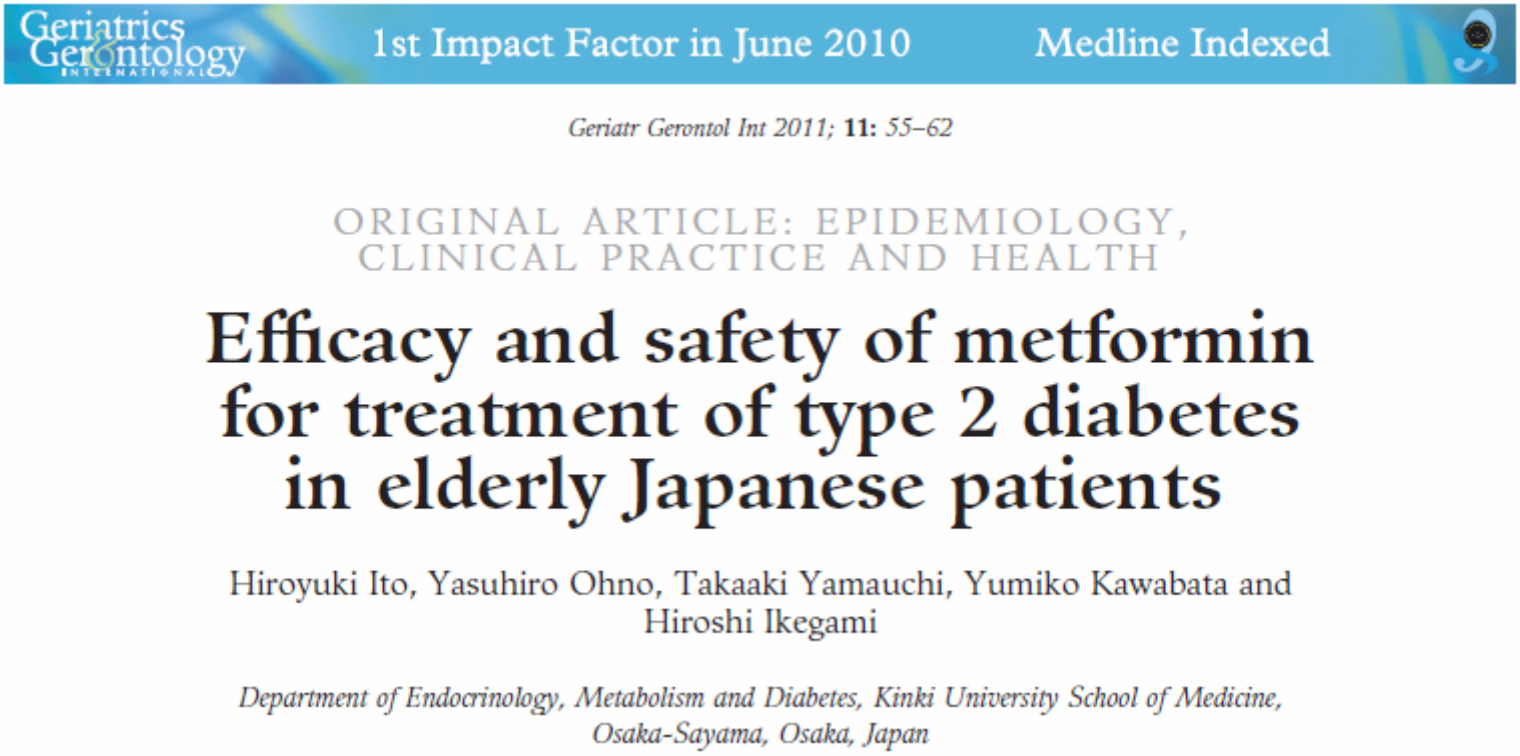


Fig. 2. Age- and sex-adjusted rates of mortality and hospitalization among patients with heart failure and new-onset diabetes mellitus, by therapy with metformin.



- Retrospective study in Japan to study efficacy of newly prescribed metformin in 568 patients from 2001 to 2006
- 180 patients (31.7%) were age 65 years or over

- Efficacy of metformin in Japanese elderly patients with type 2 DM is not different from that in non-elderly patients
- Efficacy was independent of age, sex, degree of obesity and concomitant use of other drugs
- No lactic acidosis was observed
- Safety might be linked to specific contraindications rather than age itself

MALA - Truth or myth?

- No evidence from existing literature that metformin increases the risk of lactic acidosis when compared with other anti-hyperglycaemic agents
- DM per se is proposed to be risk factor for lactic acidosis
- Metformin is theoretically a perpetuating factor for lactic acidosis in high risk patients
- May also be an ‘innocent bystander’
- Difficult to evaluate the degree of contribution to lactic acidosis by metformin in high risk DM patients

Conclusion

- Large prospective and comparative trials in type 2 DM patients with traditional contraindications to metformin may be the direction of future research
- Current evidences suggest metformin is safe in stable stage 1 and 2 chronic kidney disease, well compensated heart failure and old age
- Instead metformin should be stopped in case of acute illness which may predispose to acute renal failure or hypoxia condition
- Little evidence regarding metformin use in patients with liver disease or receiving IV contrast media

Back to our patient…

- Calculated CrCl before admission = 44.5 ml/min
- Has to balance the risk and benefit before restart of metformin
- Our patient has psychiatric illness and relatively suboptimal self-caring ability
- May not able to stop metformin in case of acute illness such as sepsis, ACS, dehydration or GE
- Metformin was discontinued upon discharge form hospital
- RFT was static with latest Cr 98

Back to our patient…

- Lactic acidosis in our patient is likely precipitated by dehydration (possible GE), acute renal failure and perpetuated by continuation of metformin in underlying DM