HOW to PRESCRIBE METFORMIN in PATIENTS with CKD2-3A-3B-4

Quid Lactic Acidosis ?

Metformin as renoprotector ?

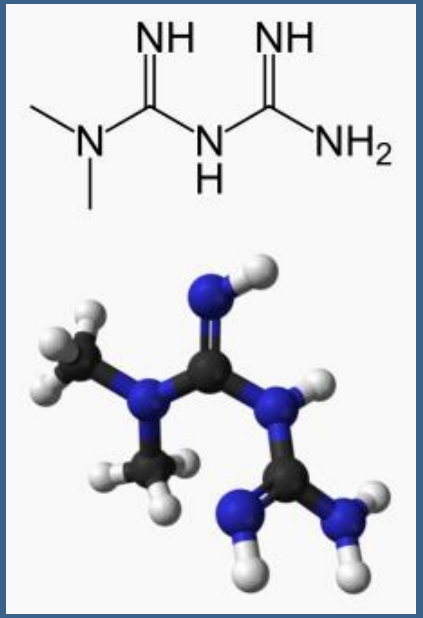
marc de broe

Laboratory of Pathophysiology, University of Antwerp, Belgium

Budapest 2018

Universiteit Antwerpen

Metformin (Glucophage) Biguanide



- Metformin (129 mw) It **is the first-line drug of choice for the treatment of type 2 diabetes**, in particular, in overweight and obese people and those with normal kidney function.

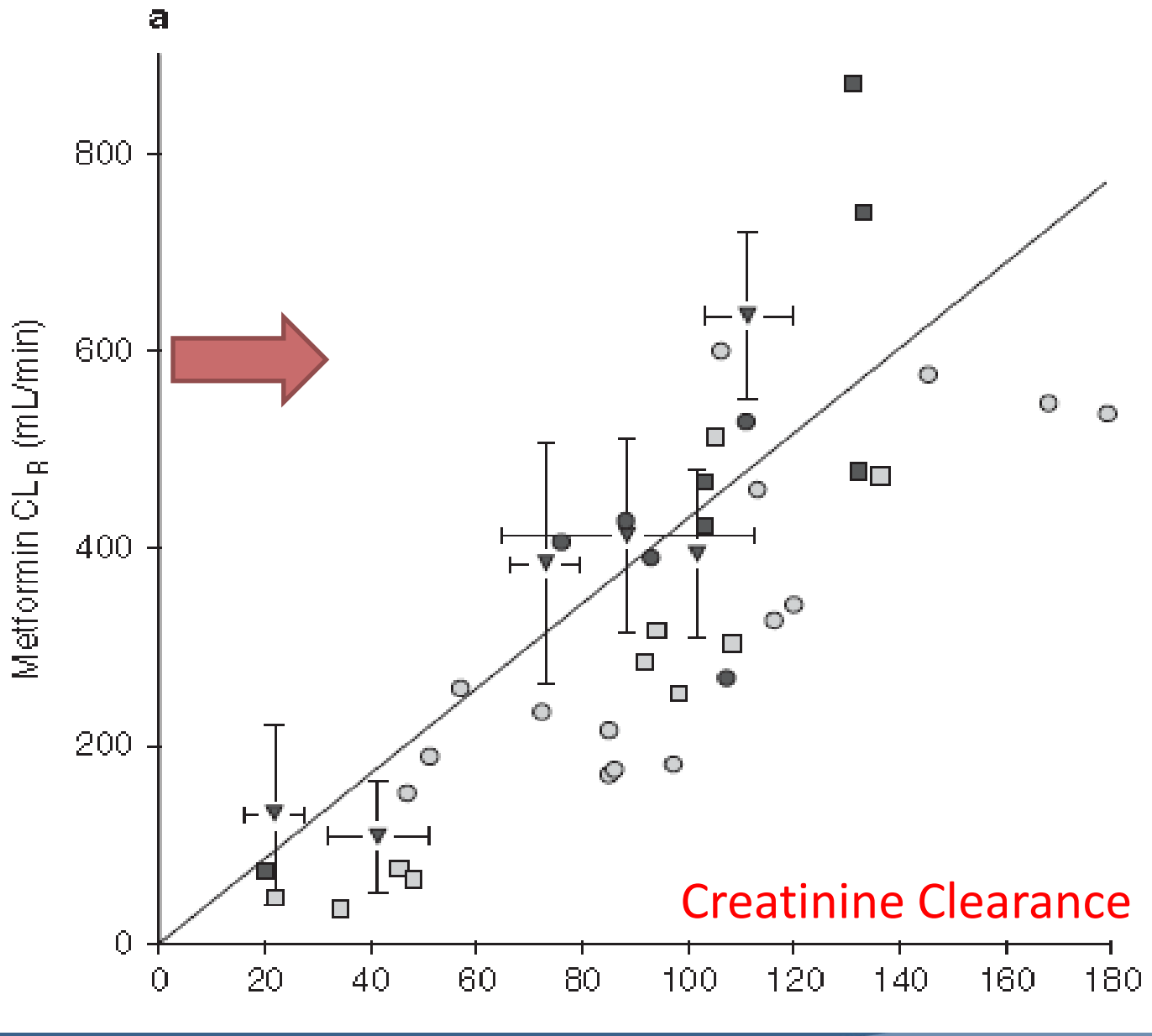
- Metformin is **one of only two oral antidiabetics in the World Health Organization Model** List of Essential Medicines

- Metformin is not metabolized, non protein bound, organic cation.
- Cleared by **GF and tubular secretion (550 ml/min)** and excreted **unchanged** in the urine. The average elimination half-life in plasma is 1.5hrs hours. Metformin is present red blood cells, with a much longer elimination half-life: 17.6 hours.

Goat Rue
Galega Officinalis
G. officinalis has been (biguanides)
known since the Middle Ages for relieving the symptoms of diabetes mellitus.

Pharmacological activity of Metformin

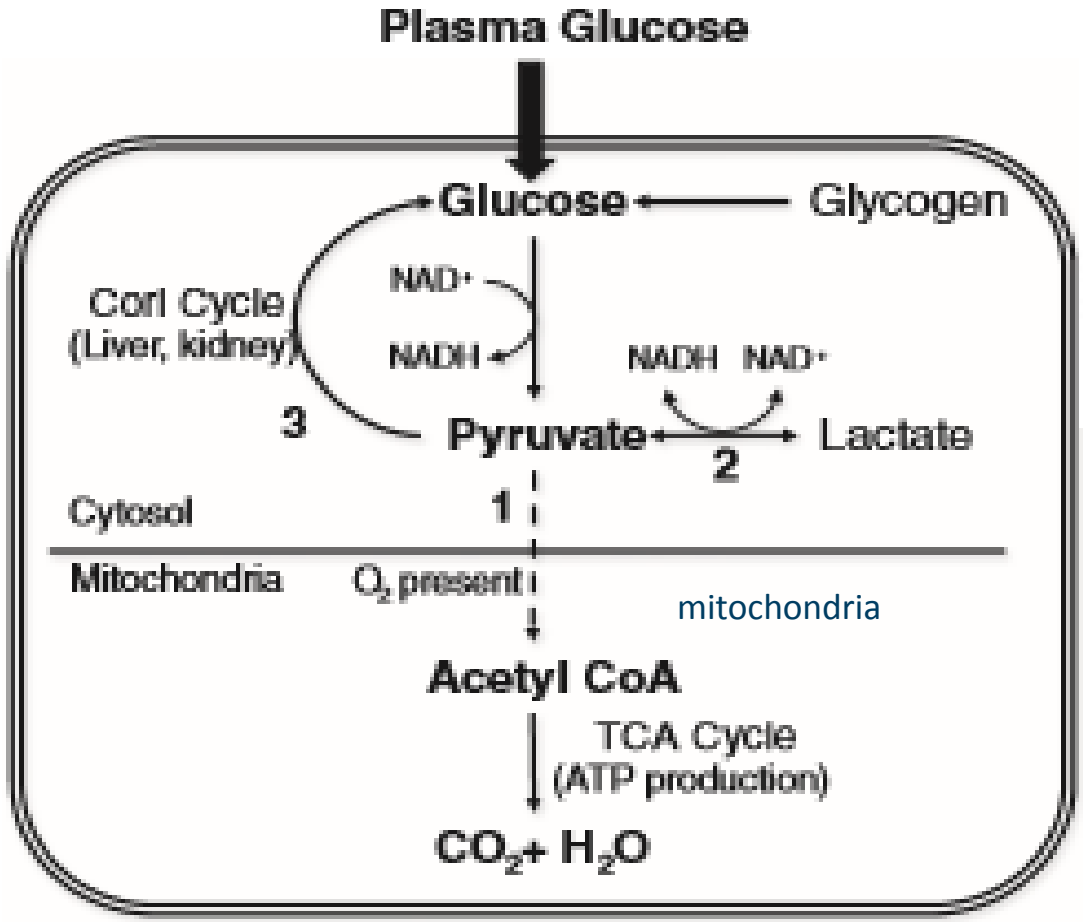
- ↓ gluconeogenesis in the liver
- stimulation of glucose uptake in the muscle
- ↑ free fatty acid oxidation
- ↓ free fatty acid synthesis
- peripheral insulin sensitivity improved
- (inhibition of the mitochondrial respiratory chain complex 1)

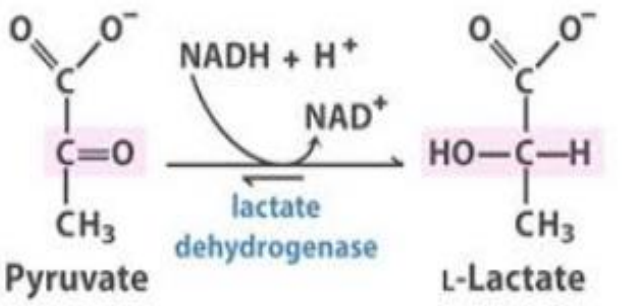


Tucker GT ..1981 +
Pentikänen PJ.. 197
Sirtori CR.. 1978 ++
Sambol NC.. 1995 +
Noel M .. 1979

Compilation of literature

Graham G et al Clin Pharmacokinet 50; 81, 2011





Biochemistry of lactate production. Pyruvate, the only precursor to lactate, is produced in the cytoplasm from metabolism of glucose via glycolysis.

(1)Glycolisis. When oxygen is available, pyruvate enters the mitochondria and is oxidized to CO2 and H2O in the TCA cycle. During ATP hydrolysis protons are produced , are incorporated in new formed ATP ,maintaining pH

(2) Under anaerobic conditions, pyruvate is unable to enter the mitochondria to be oxidized and is reduced to lactate, electroneutrality requires a cation (protons) , **protons generated from glycolysis are no more incorporated , reducing pH in the serum**

3) In the liver and kidney, pyruvate also can be converted to glucose . DeFronzo Metabolism 2016the blood

Lactic acidosis

Arterial lactate 0.5 – 1.6 mmol/L

Hyperlactatemia 2 – 5 mmol/L

Diagnosis LA lactate > 5 mmol/L pH < 7.33 Anion gap

$HCO3^{--}$ ↓ or low normal

Type A

- LA clinical evidence of inadequate tissue perfusion oxygenation
- glycolysis in absence of oxygen (shock, sepsis, CO intox, anemia)

Type B

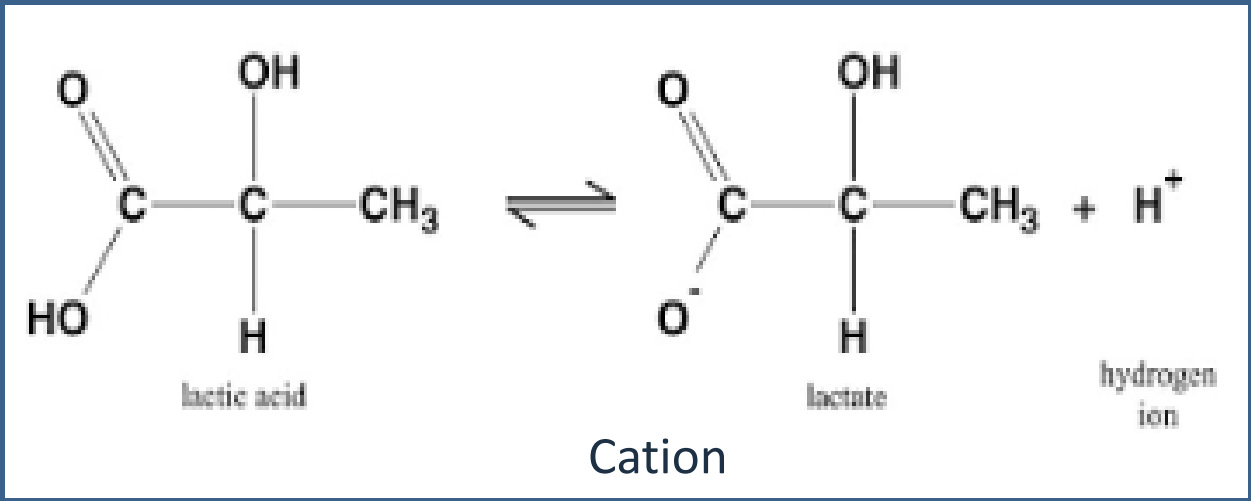
- no clinical evidence of poor tissue perfusion
- lactate production increased associated with ↓ lactate clearance

B1 – underlying disease (ketoacidosis)

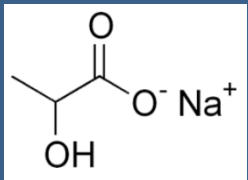
B2 – drugs (metformin, salicylates, alcohol)

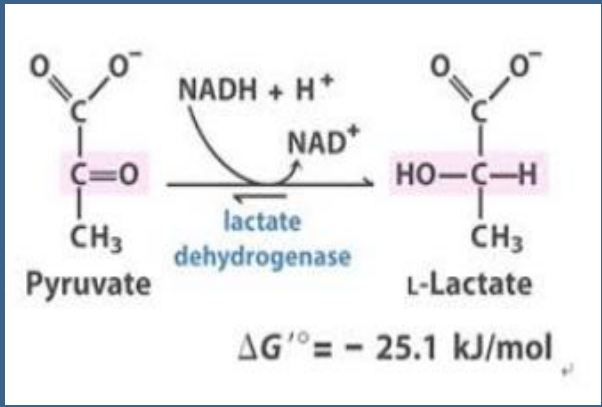
B3 – errors of metabolism (pyruvate dehydrogenase def.)

MULA MILA MALA


lactic acid
lactate
hydrogen ion

Cation



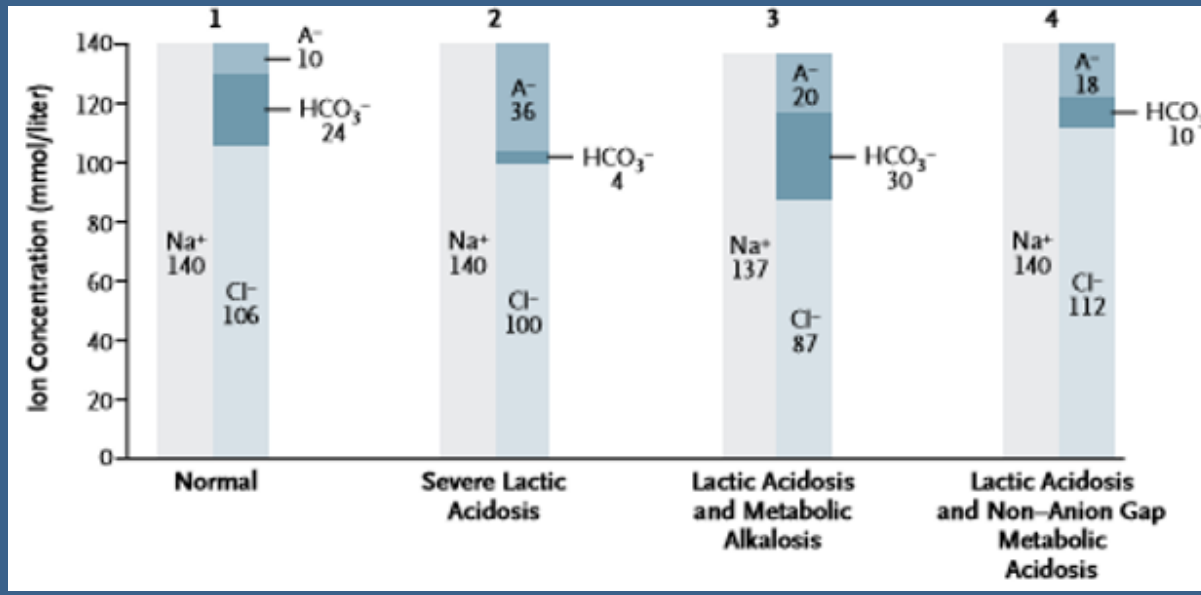

NADH + H+
NAD+
lactate dehydrogenase
Pyruvate
L-Lactate
ΔG'° = − 25.1 kJ/mol

ANION GAP (Na+) - (Cl +HCO3) =

Normal serum values 8 –12 mEq/L

An elevated anion gap (>12 mEq/L), >5mmol/L , Blood pH < 7.3

- Methanol
- Uremia
- Diabetic ketoacidosis
- Propylene glycol
- Isoniazid intoxication
- Lactic acidosis
- Metformin
- Ethanol ethylene glycol
- Rhabdomyolysis/renal failure
- Salicylates



FDA **5 mg/l**…."safety level "

mean plasma concentrations of metformin over a dosage interval be maintained **below 2.5mg/L (Cav , ss)**

NEJM december 2014 Kraut et al

Metformin induced associated lactic acidosis (MILA, MALA) (1)

- Lactate > 5 mmol/L Blood pH < 7.33 Anion gap > 15 mEq/L
  eGFR! Therapeutic doses of M, and no CKD, lactate levels < 2 mmol/L

- Metformin lactic acidosis :
- Shift intracellular redox potential , from aerobic ot anaerobic metabolism
- Suppresion of hepatic gluconeogenesis from lactate

- M inhibits mitochondrial respiration in tissues (complex 1) responsible for lactate removal/metabolism (liver, muscle)

- In**creased production of L pyruvate → lactate, free protons**
  Decreased metabolism of L ↓ oxidation ↓ gluconeogenesis
  = LACTATE ↑ in serum ↑ protons ↑ acidosis

CKD is a major risk factor why??

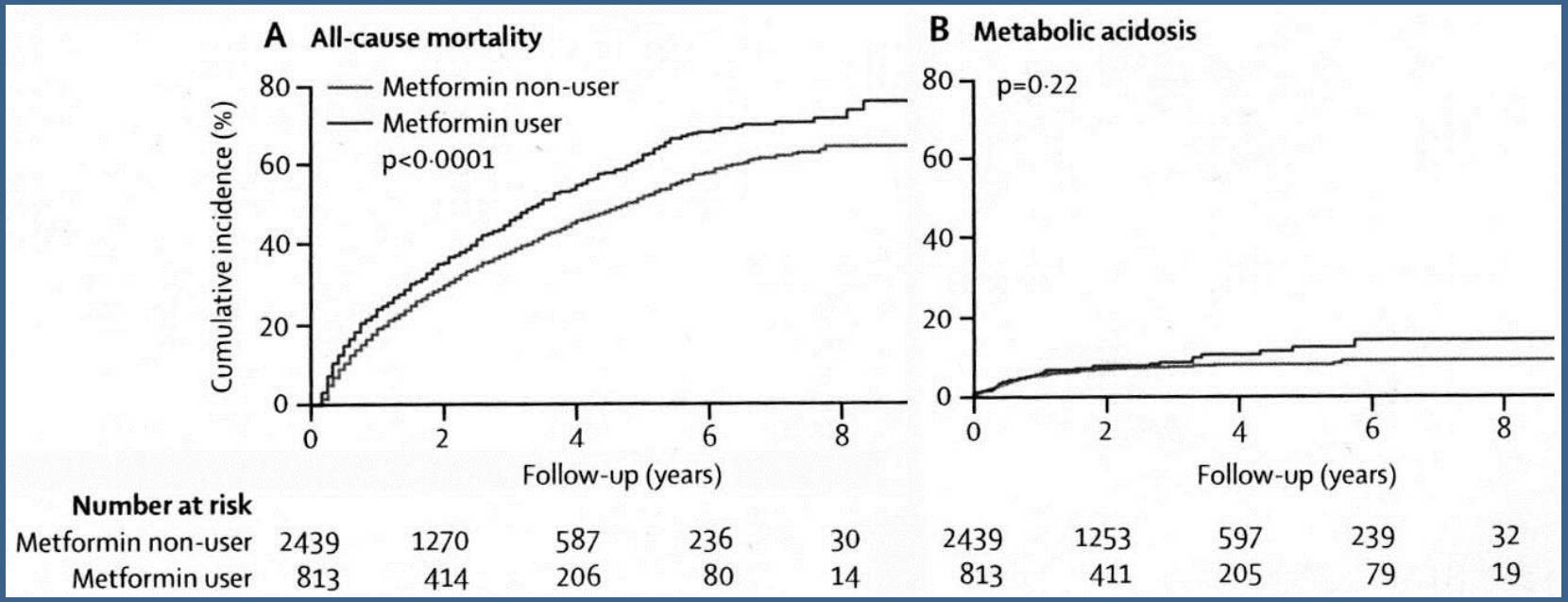
Metformin associated lactic acidosis (MALA)

- Salpeter S (2010): Cochrane review: no case of MALA in 70 490 p/y metformin
- Bodmer M (2008): UK, GPRD nested case control MALA: 3.3 m+ 4.8 SUR 100 000 p/y
- Ekström N (2012): type 2 diabetes cohort: next
  45-60 eGFR lower risk of LA, infection
  30-45 eGFR insignificant higher risk
- Eppenga W (2014): UK,GPRD LA - clinical > 5 mmol/L
  incidence 7.4 m+ 2.2 m- / 100 000 p/y
  Comments Inzucchi
- Hung S (2015): Taiwan NHID CKD5 diabetic patients
  35% higher mortality risk m+ / m- no increase of lactate level
  Comments Lalau, De Broe

Salpeter SR et al, Cochrane Database Syst Rev 2010; 4:CD002967
Bodmer M et al: Diabetes Care 2008; 31:2086-91
Ekström N et al: BMJ open 2012; 2:e001076
Eppenga W et al: Diabetes Care 2017; 37: 2218-24
Hung SC et al: Lancet Diabetes Endocrinol 2015; 3:605-14

Mortality and metabolic acidosis

CKD 5 high risk



Type 2 diabetes and CKD5

Hung SC et al: Lancet Diabetes Endocrinol 2015; 3:605-14

No reporting of cause of dead, metformin conc, doses, associated drugs, co- morbidities

.....

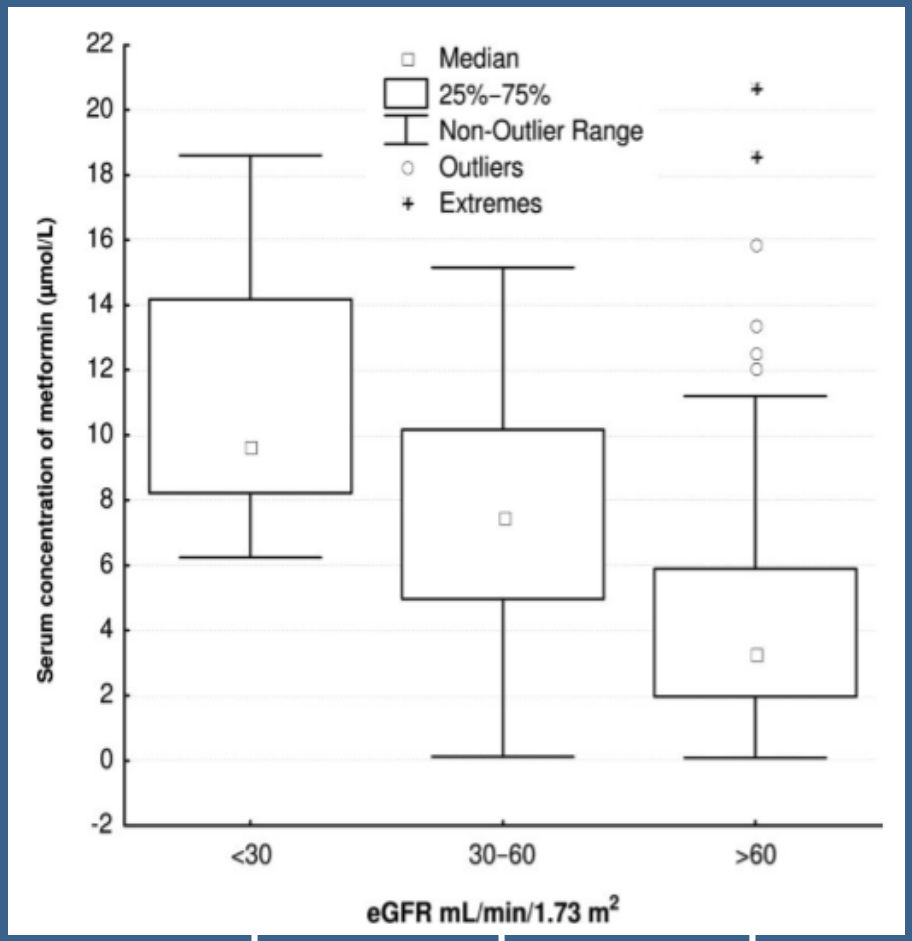
The relationship between metformin and lactic acidosis MALA MILA

- • The risk of lactic acidosis is essentially nil in the context of clinical trials, including those that did not specify kidney disease as an exclusion criterion
- • The incidence of lactic acidosis in the setting of metformin therapy is low, and the drug is not necessarily responsible when lactic acidosis occurs in patients taking this medication.
- • There may have been underestimation of MALA risk due to confounding by indication; and that, conversely, ascertainment of MALA using lactate levels may have overestimated the risk.

- • A conservative synthesis of these data is that, as long as kidney function is stable and the patient is observed closely, metformin is unlikely to measurably increase the risk of lactic acidosis in patients with moderate CKD (i.e., eGFR 30-60 mL/min/1.73 m^2). **Cave CKD5** !!!

Inzucchi S et al: JAMA 2014, 312, 2668-75 Systemic review of lactic acidosis in CKD patients 1950-2014

CHAOTIC USE



Trough levels

500-3000 mg/day

Median levels:	8.9	7.7	4.5	µmol/l	
	1.4	1.2	0.7	mg/L	5mg/L!!!!!

Frid A et al Diabetes Care 33; 1291-1203, 2010
Seven out of 137 patients developed lactic acidosis (mean 52.8 mg/L)

Metformin (Met) induced lactic acidosis (MILA MALA) (2)

Correlation between increased Met levels and decreased pH

High lactate levels and low pH predictors of fatal outcome

- Frieseke et al, 2011
  - 10 Met LA –renal failure
  - pH 6.75, lactate 19 mEq/L
  - S.A.P.S. II 88 ± 23 predicted mortality 96% hospital survival 50%
  - 31 severe LA not related to met (CV, sepsis, ...) no survivor
- Labarr GD, 1999
  - 49 pts MILA
  - survival 17% no drug accumulation (not Met related)
  - survival 79% Met accumulation
- Yirenda, 2006
  - 1 out of 10 † with LA + Met accumulation
  - predicted mortality 55%
- Prati A et al, 2010
  - 24 LA met intoxication
  - S.A.P.S.II 87, predicted mortality 70%, actual mort . 21%
  - pH 6.62, lactate 33 mEq/L
  - **Protection** of **Metformin**

Simplified Acute Physiology Score

Table 1 | Laboratory data of the patients on admission

Initial presentation	Patient 1	Patient 2	Reference values
Arterial blood gas			
pH	7	6.78	7.35–7.45
pCO_2 (mm Hg)	7	15	35–45
tCO_2 (mEq/l)	2	3	—
Serum Electrolytes			
Na^+ (mEql/l)	133	146	136–145
K^+ (mEq/l)	6.7	6.6	3.5–5.5
Cl (mEq/l)	102	100	96–110
HCO_3 (mEq/l)	5	5	24–32
Anion Gap	26	41	8–12
Corrected Ca^{2+} (mEq/l)	9.1	9.0	8.5–10.5
Phosphate [PO_4^-] (mg/dl)	8.1	13.6	2.5–4.5
Serum blood urea nitrogen (mg/dl)	120	32	10–26
Serum glucose (mg/dl)	184	143	70–100
Serum creatinine (mg/dl)	8.9	5.9	0.7–1.5
Serum lactate (mg/dl)	9.6	22	0.7–2.1
Serum metformin level (μg/ml)	17	31	1–2
Aspartate aminotransferase (AST) (U/l)	36	242	8–50
Alanine aminotransferase (ALT) (U/l)	27	87	15–75
Complete blood count			
White Blood Cells K/cmm	11.7	40	4–10.4
Hemoglobin (gm/dl)	10.5	12.1	13.8–17.3
Platelets K/cmm	220	486	141–320

Kidn Intern 72;1157;2007

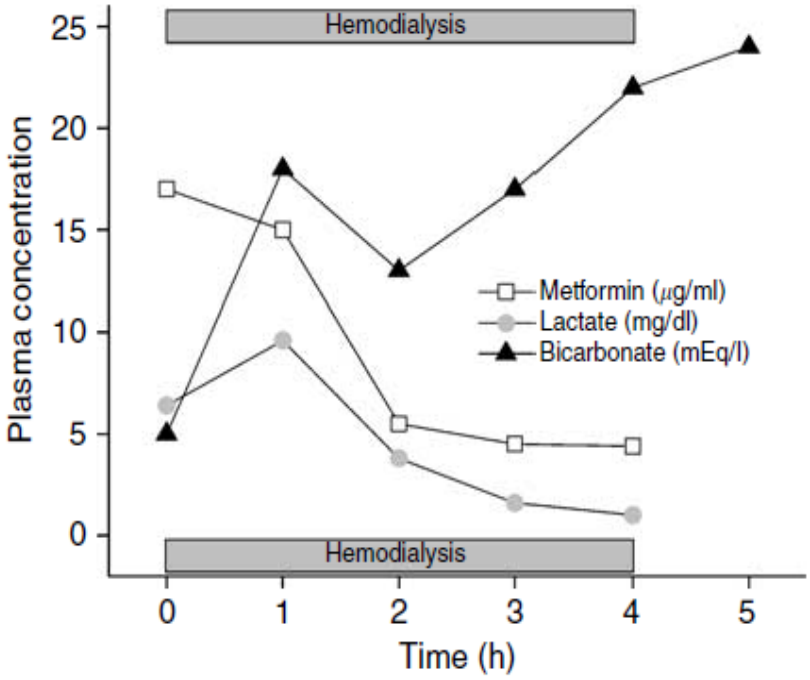


Figure 1 | Effect of intermittent hemodialysis for 4 h on serum lactate, metformin, and bicarbonate levels. Note the rapid decrease of both metformin and serum lactate level and the reciprocal increase of the bicarbonate level.

Kidn Intern 72; 1157; 2007 M Prikis et al

Treatment
Elimination of the drug (metformin)
Correcting acid- base imbalance
Treating concomitant disease

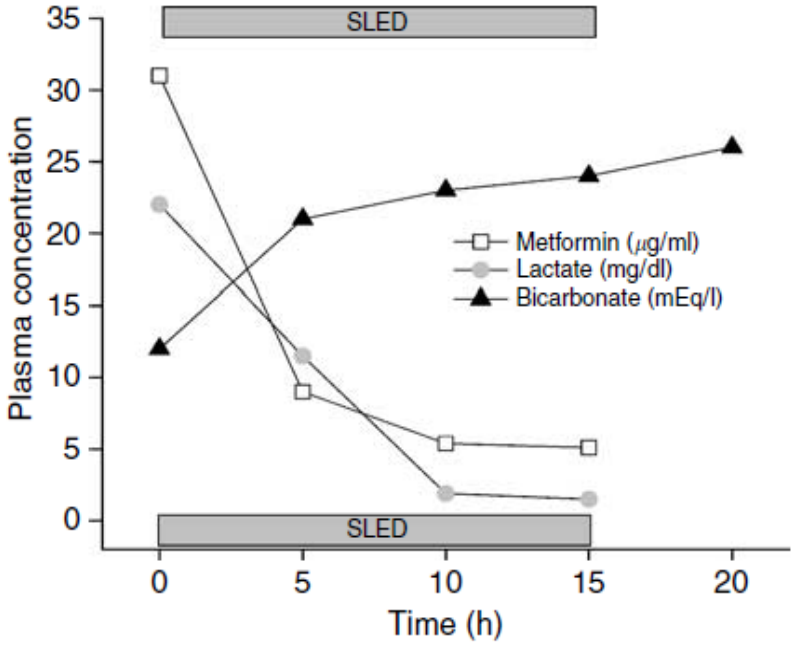


Figure 2 | Effect of sustained low-efficiency dialysis (SLED) over 15 h in the serum lactate, metformin, and bicarbonate levels. Note the rapid decrease of both metformin and serum lactate levels and the reciprocal increase of the bicarbonate level.

Metformin induced lactic acidosis (MILA MALA) (3)

- Metformin intoxication – renal replacement therapy:
  efficient removal of the toxic substance:
  prognosis can be surprisingly good

- Veno-venous hemodiafiltration + bicarbonate
- Sustained low-efficiency dialysis (SLED)
- No peritoneal dialysis (lactate)

Comparison of Recommendations

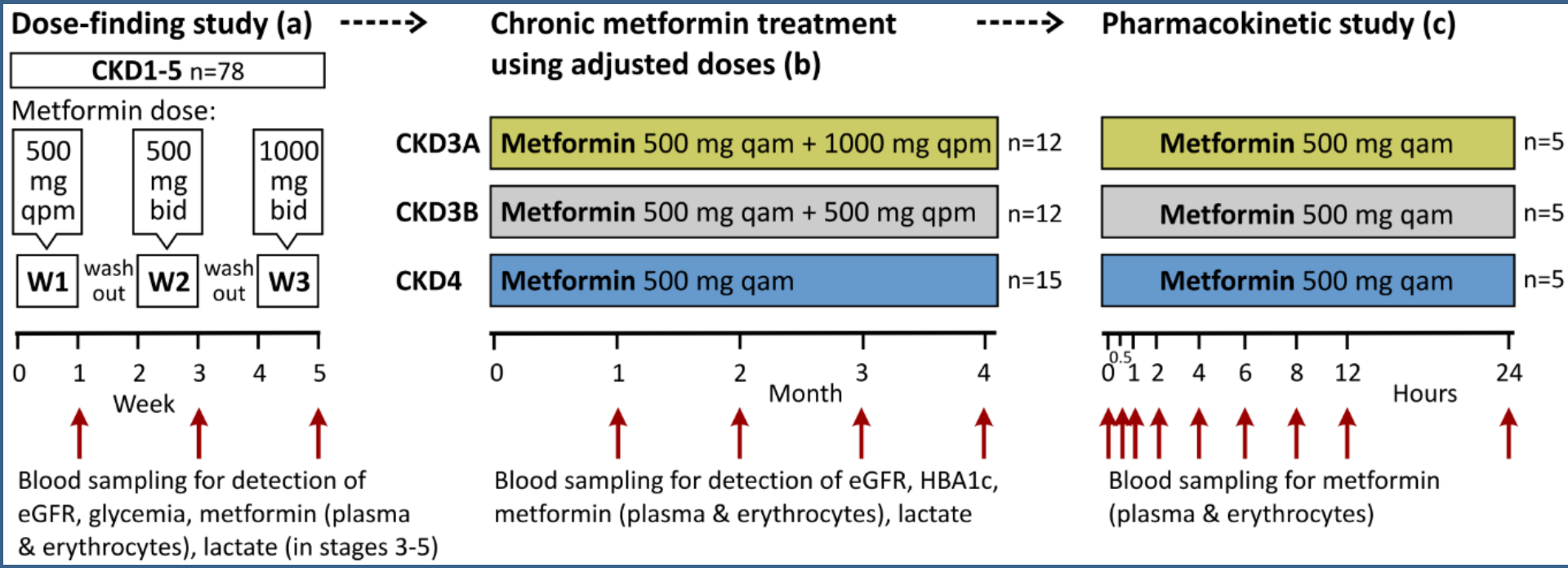
	Absolute Contraindication	Dose Adaptation / Caution
Current Product Label	Crea Clearance <60	Elderly: adaptation based on renal function
NICE	eGFR <30 Crea >150 µmol/L	eGFR <45 Crea >130 µmol/L
ADA / EASD	eGFR <30	No info
SN / SFD (France)	Crea Clearance <30	Crea Clearance 30-60
AACE /ACE	Crea Clearance <60 Crea ≥1.5 mg/dL (men) Crea ≥1.4 mg/dL (women)	No info
ACP	Impaired kidney function	No info
Canadian Nephrology	CKD stage 4 and 5 (GFR <30)	CKD stage 3 (GFR 30-59)
Diab Australia /NHMRC	eGFR <30	eGFR 30-45

FDA Drug Safety Communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function

- April 2016. We have concluded from the review of studies published in the medical literature that metformin can be used safely in patients with mild impairment in kidney function and in some patients with moderate impairment in kidney function.[3-6] We are requiring changes to the metformin labeling to reflect this new information and provide specific recommendations on the drug's use in patients with mild to moderate kidney impairment. (CKD 3A 3B)

- EMA october 2016 : the large patient population with moderarely reduced kidney function can benefit fom use of metformin. The contraindication for patients with severely reduced kidney function will remain (eGFR less than 30ml/min)

- Dose adaptation ??



Metformin Treatment in Patients With Type 2 Diabetes and Chronic Kidney Disease Stages 3A, 3B, or 4

Jean-Daniel Lalau,[1,2] Farshad Kajbaf,[1,2] Youssef Bennis,[3] Anne-Sophie Hurtel-Lemaire,[3] Frans Belpaire,[4] and Marc E. De Broe[5]

https://doi.org/10.2337/dc17-2231

Diabetes Care 41, 547, 2018

Therapeutic concentrations of metformin
A systematic review

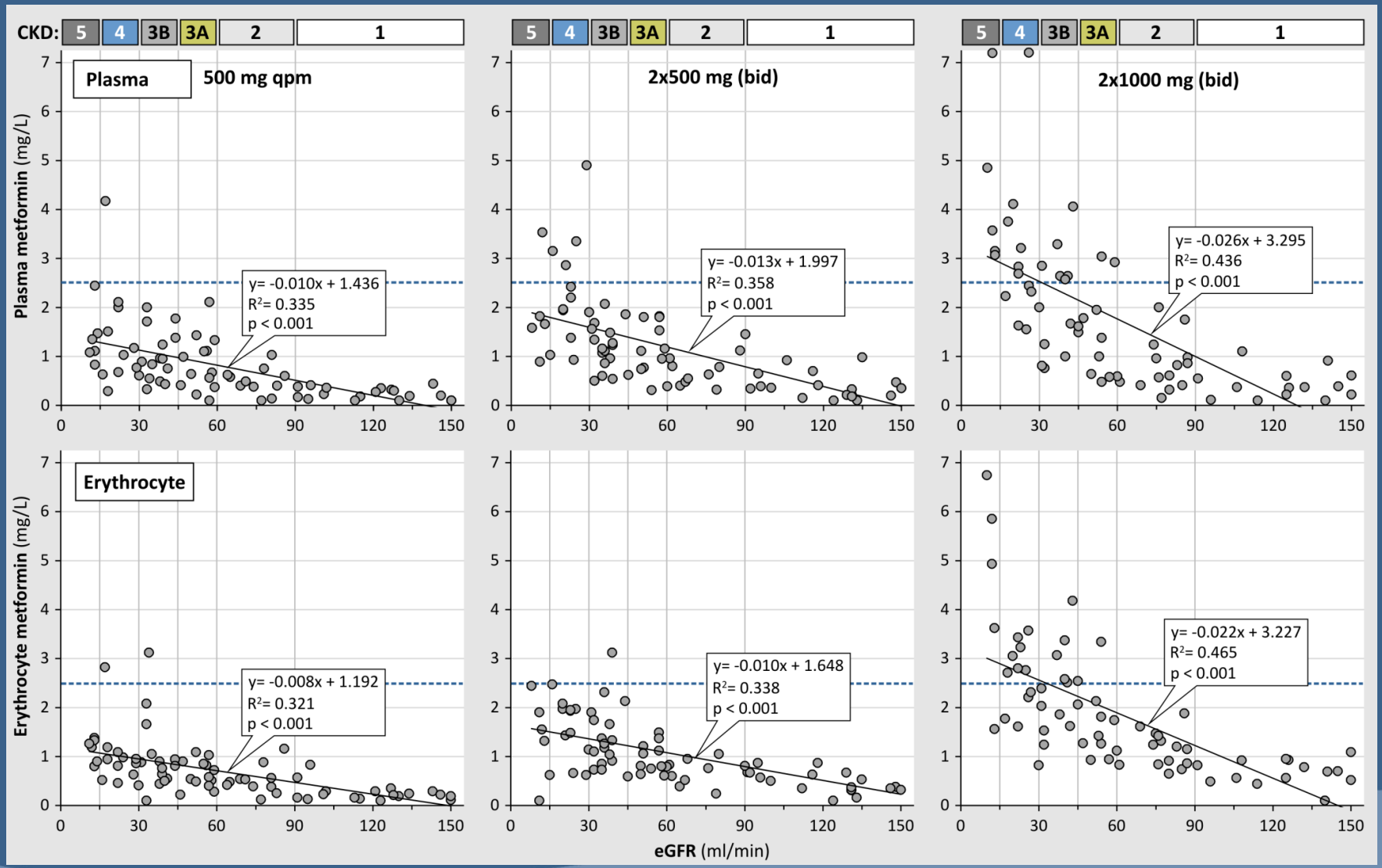
- FDA **5 mg/l**…."safety level "
- mean plasma concentrations of metformin over a dosage interval be maintained **below 2.5mg/L** (Cav, ss)

- plasma lactate begins to increase when plasma metformin concentrations are greater than about **20mg/L**
- Lactate levels **< 5mMol**

Kajbaf F, De Broe, M Lalau JD. Clin Pharmacokinet 2015 «CPKA-D-15-00143(1)» 2015

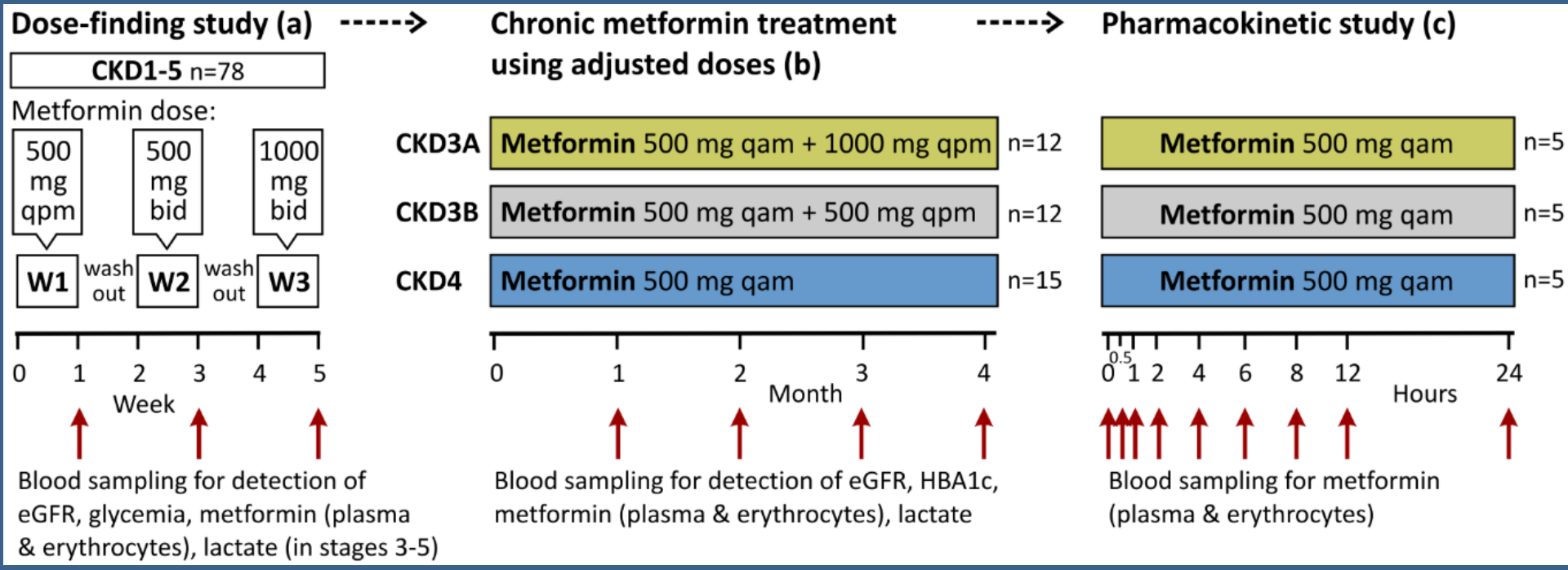
Dose finding trough level 12hrs after dose

Saturation of tubular secretion
Steaper slope

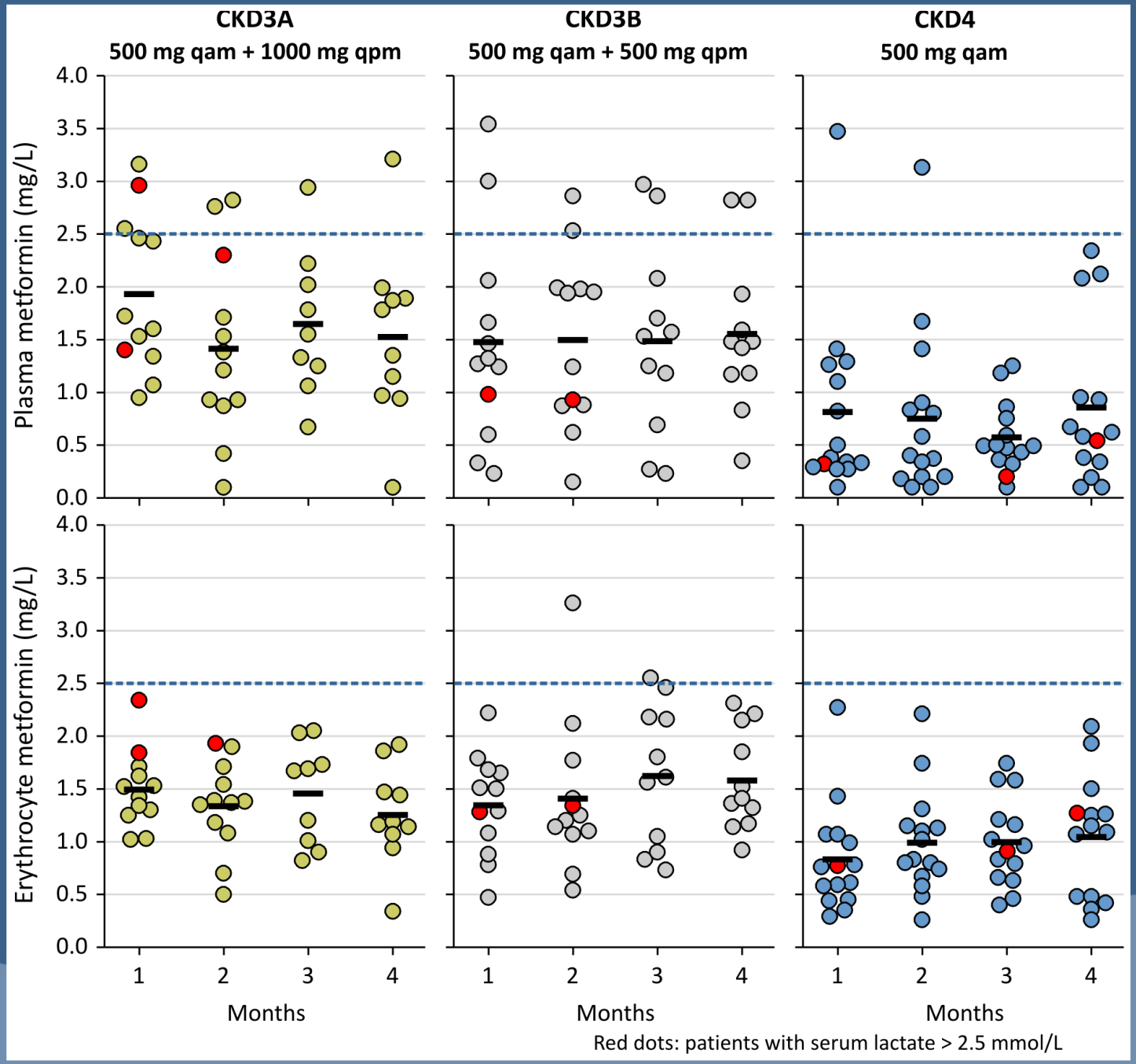


Correlation metformin in plasma/erythrocyte vs. eGFR
<5mg/l FDA safe concentration

Diabetes Care Lalau et al 41; 547-553, 2018



Diabetes Care Lalau et al 41; 547-553, 2018



12 hr after the last dos

Below 5mg /L

?

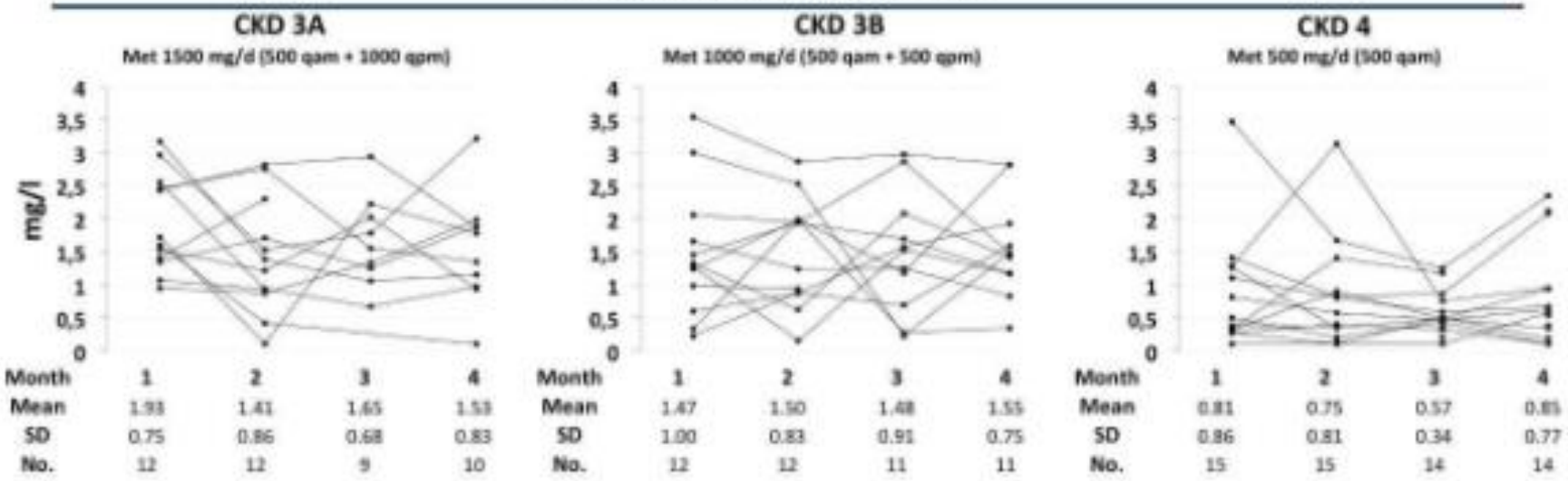
Lactic Acidosis > 5mMol
pH < 7.35

Diabetes Care Lalau et al
41; 547-553, 2018

A 4 month-metformin therapy in CKD with adjusted dose

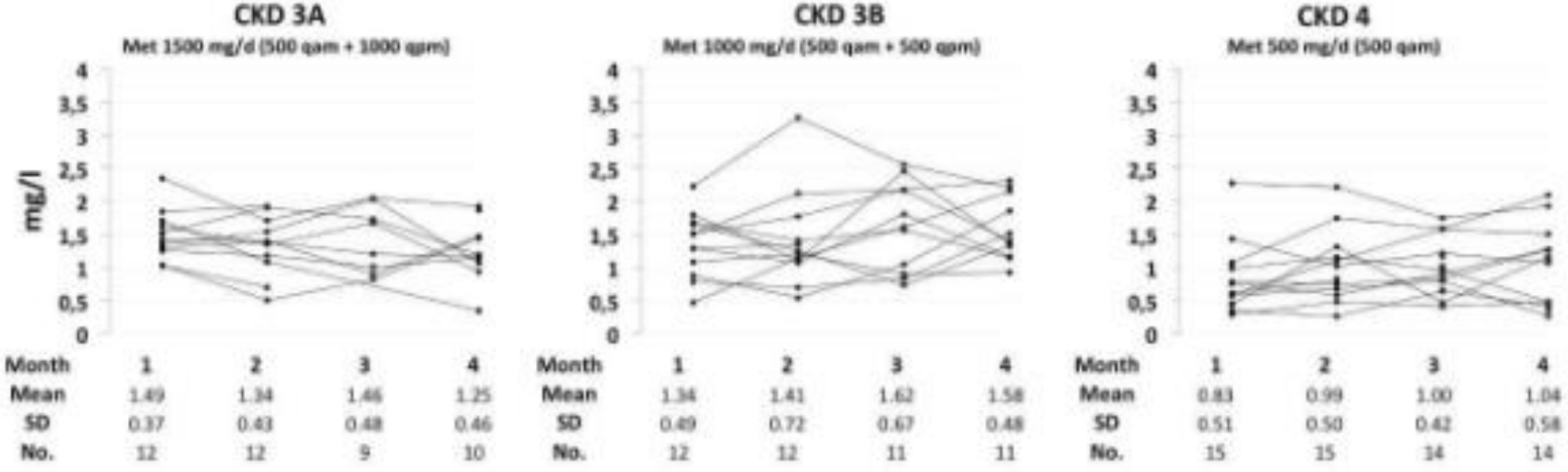
OCT transporters

1- Plasma metformin concentrations

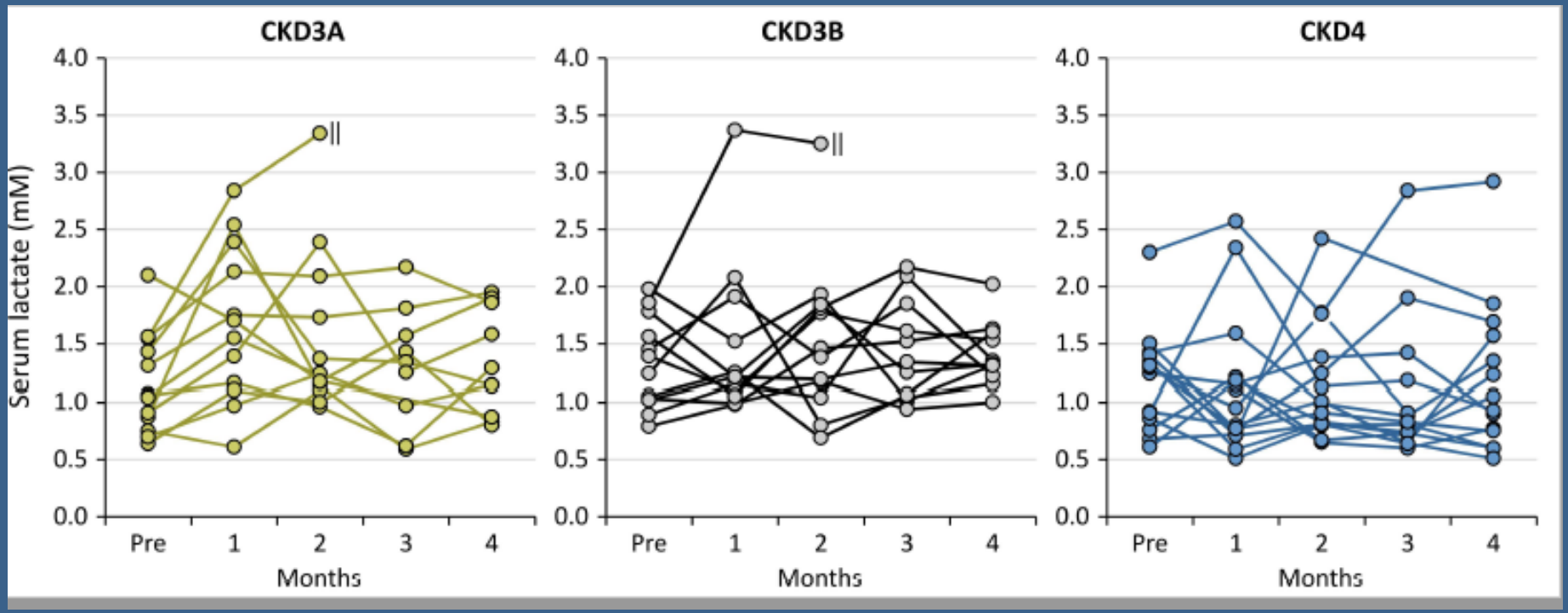


	CKD 3A				CKD 3B				CKD 4			
Month	1	2	3	4	1	2	3	4	1	2	3	4
Mean	1.93	1.41	1.65	1.53	1.47	1.50	1.48	1.55	0.81	0.75	0.57	0.85
SD	0.75	0.86	0.68	0.83	1.00	0.83	0.91	0.75	0.86	0.81	0.34	0.77
No.	12	12	9	10	12	12	11	11	15	15	14	14

2- Erythrocyte metformin levels

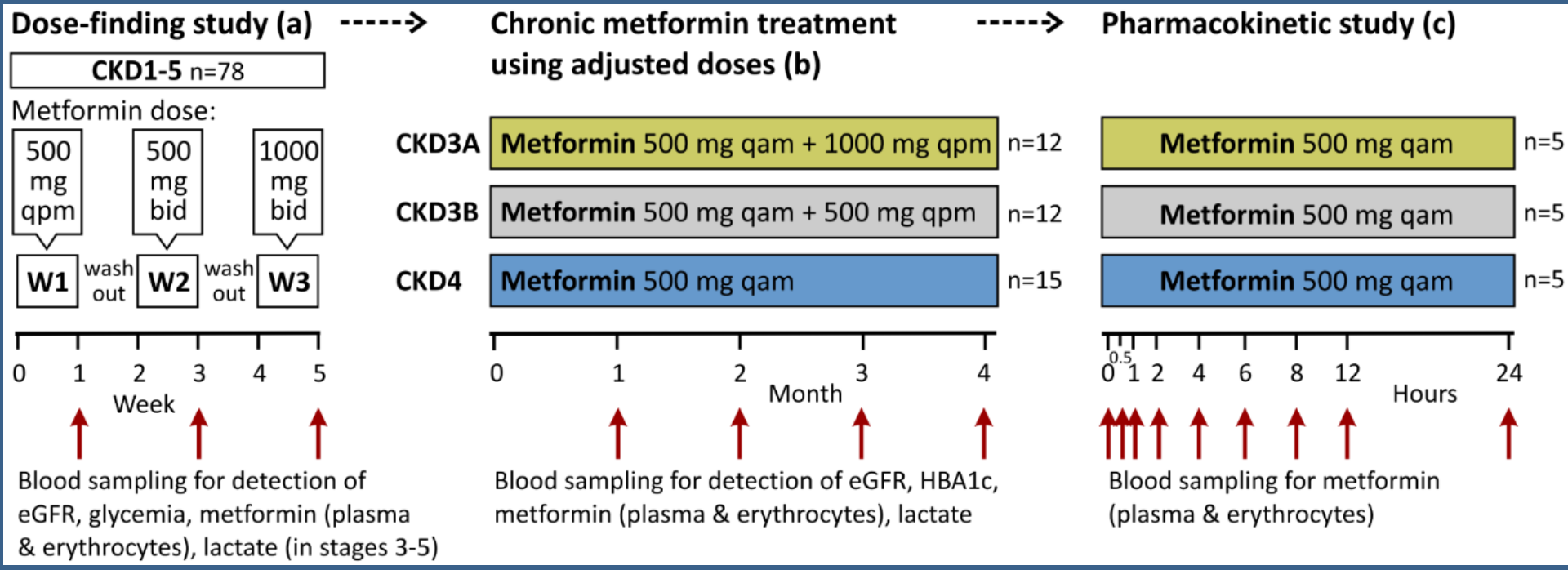


	CKD 3A				CKD 3B				CKD 4			
Month	1	2	3	4	1	2	3	4	1	2	3	4
Mean	1.49	1.34	1.46	1.25	1.34	1.41	1.62	1.58	0.83	0.99	1.00	1.04
SD	0.37	0.43	0.48	0.46	0.49	0.72	0.67	0.48	0.51	0.50	0.42	0.58
No.	12	12	9	10	12	12	11	11	15	15	14	14



Lactic Acidosis > 5mMol ; pH < 7.35

Diabetes Care Lalau et al 41; 547-553, 2018



Diabetes Care Lalau et al 41; 547-553, 2018

Table 5. Parameters of the pharmacokinetic study.

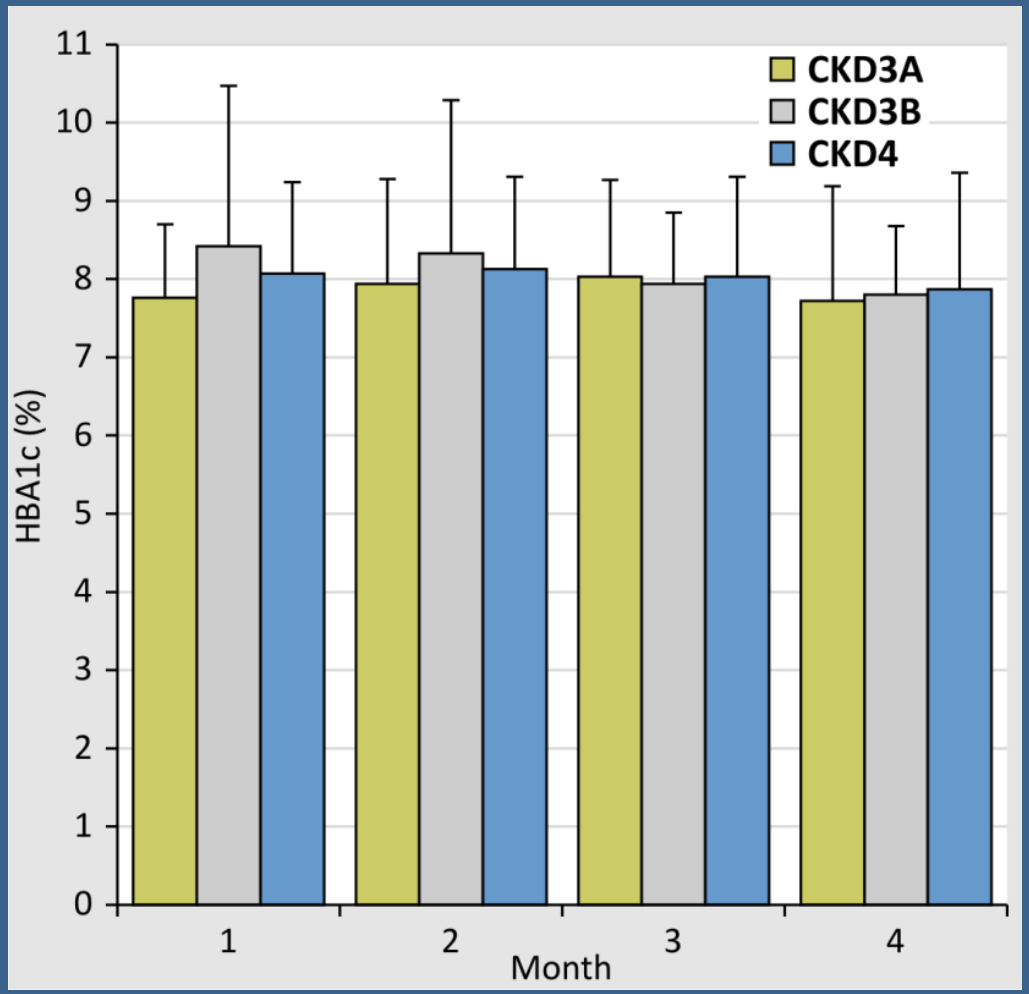
Parameters		CKD3A 1500 mg	CKD3B 1000mg	CKD4 500 mg	Comparisons between the CKD stages (p-value)
AUC (mean±SD) [range] (h.mg/L)	Plasma	26.01±8.89 [14.64-35.94]	38.54±11.00 [27.78-53.19]	31.35±11.06 [16.03-44.39]	0.31
Tmax (mean±SD) [range] (h)	Plasma	3.40±1.95 [1.0-6.0]	4.20±2.49 [1.0-8.0]	4.00±00.00 [4.0-4.0]	0.88
T1/2 (mean±SD) [range] (h)	Plasma	6.88±2.8 [3.23-10.05]	7.69±1.15 [6.22-8.7]	11.10±5.87 [27.78-53.19]	0.28
Cmax (mean±SD) [range] (mg/L)	Plasma	2.13±0.57 [1.33-2.74]	3.38±1.60 [2.13-5.94]	2.30±0.83 [1.32-3.28]	0.43
Cavss 12 (mean±SD) [range] (mg/L)	Plasma	1.57±0.54 [1.00-2.17]	2.31±0.78 [1.77-3.51]	1.31±0.46 * [0.67-1.85]	0.22
	Erythrocyte	1.17± 0.20 [1.07-1.54]	1.96±0.55 [1.27-2.66]	0.96±0.62 * [0.22-1.75]	0.11

* Cavss 24 hr (mean±SD) (mg/L)

AUC = area under curve,
Cavss= concentration average at steady state

Diabetes Care Lalau et al 41; 547-553, 2018

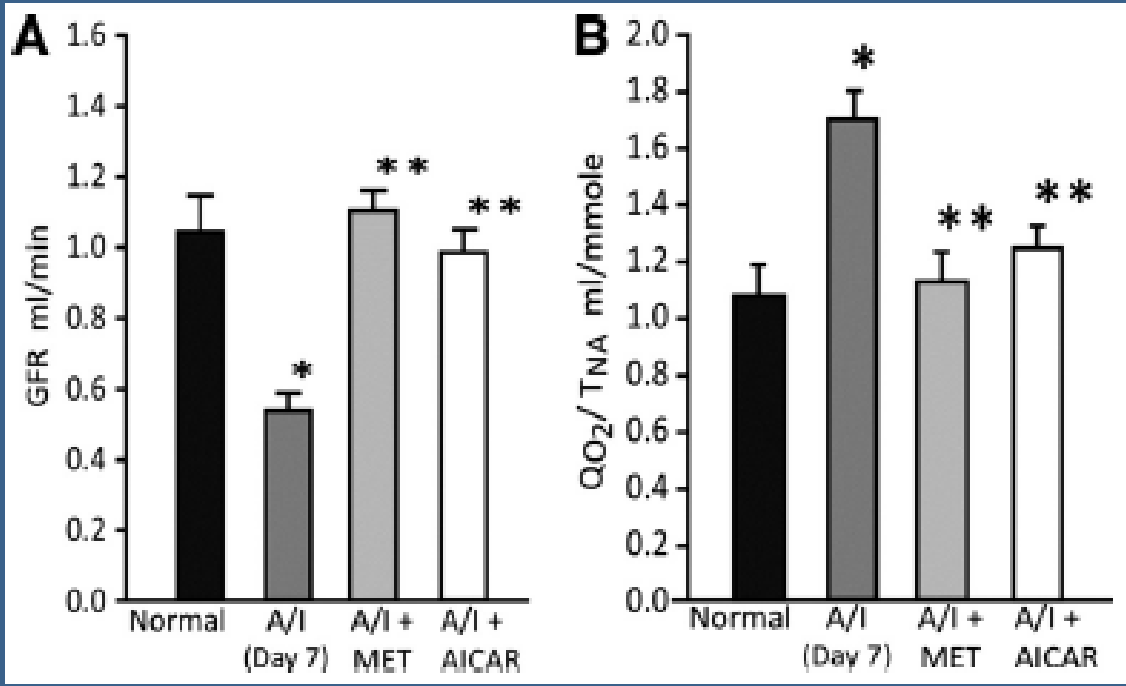
HBA1c

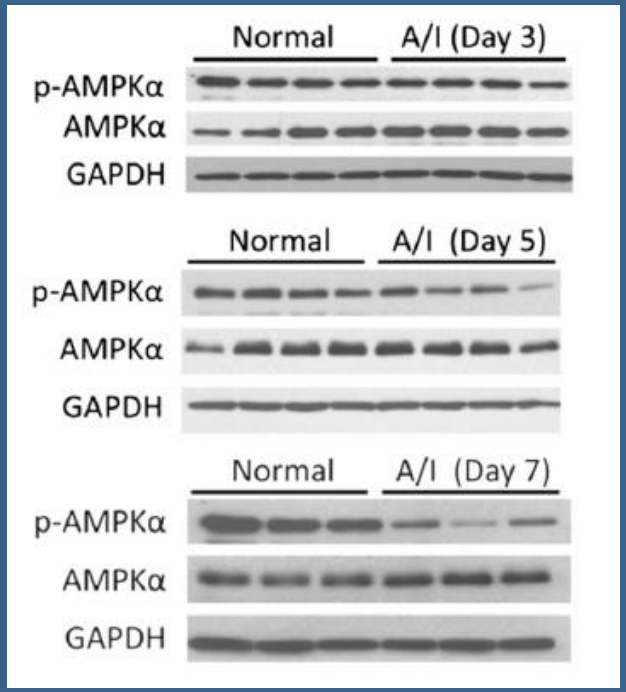


Pharmacological activity of adapted doses

Diabetes Care Lalau et al 41; 547-553, 2018

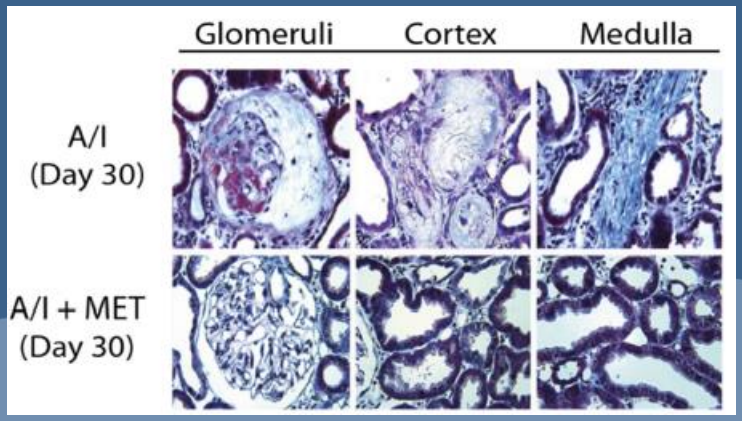
Subtotal nephrectomy “Remnant Kidney” model (rats)





We conclude that AMPK activity is reduced in the subtotal nephrectomy model of nondiabetic CKD, that altered regulation of AMPK is coincident with the progression of disease parameters, and that restoration of AMPK activity can suppress the progressive loss of function characteristic of this model

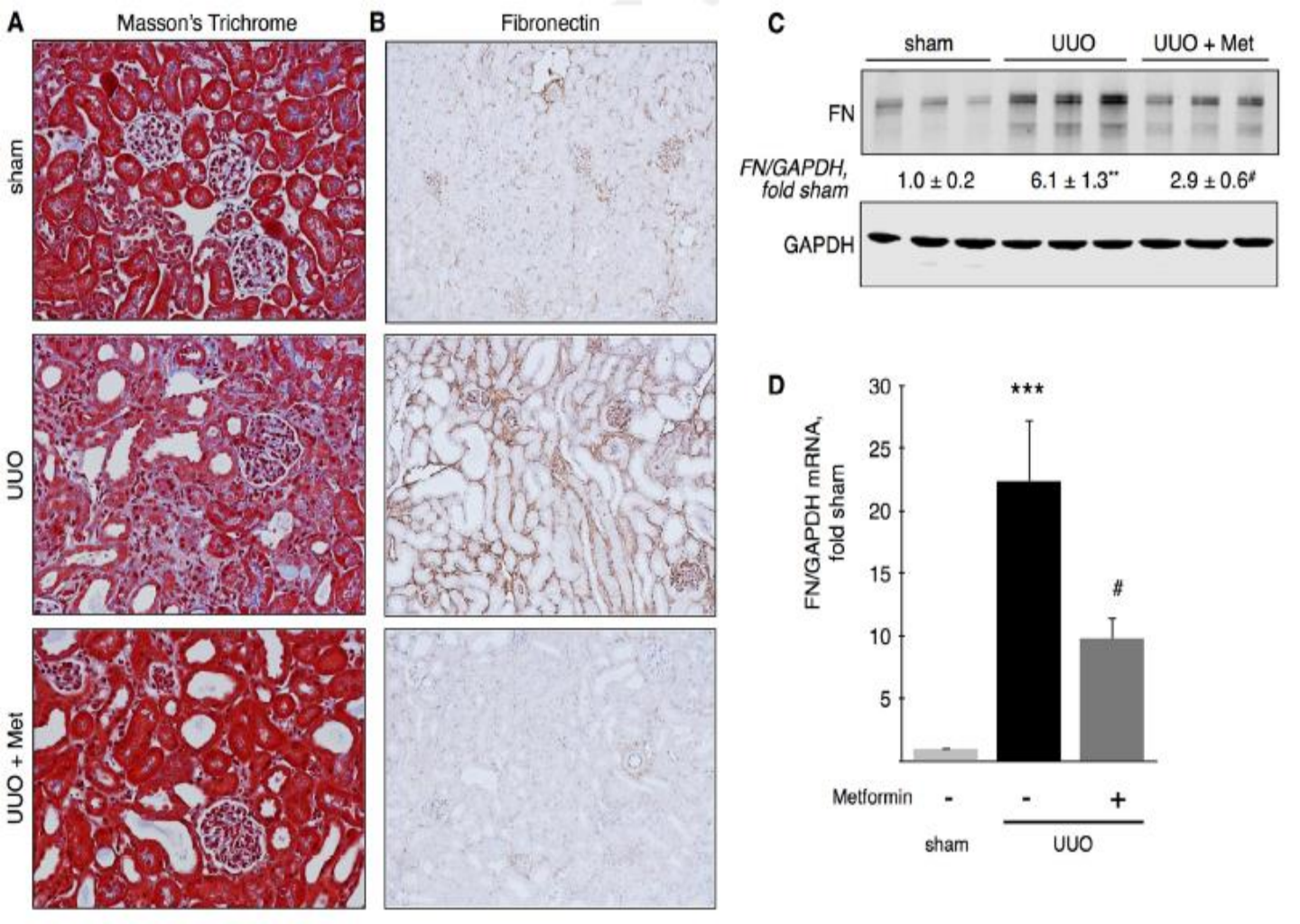
AICAR : AMPK inductor



J Satriano et al. Am J Phys. R Phys 305 , F27, 2013

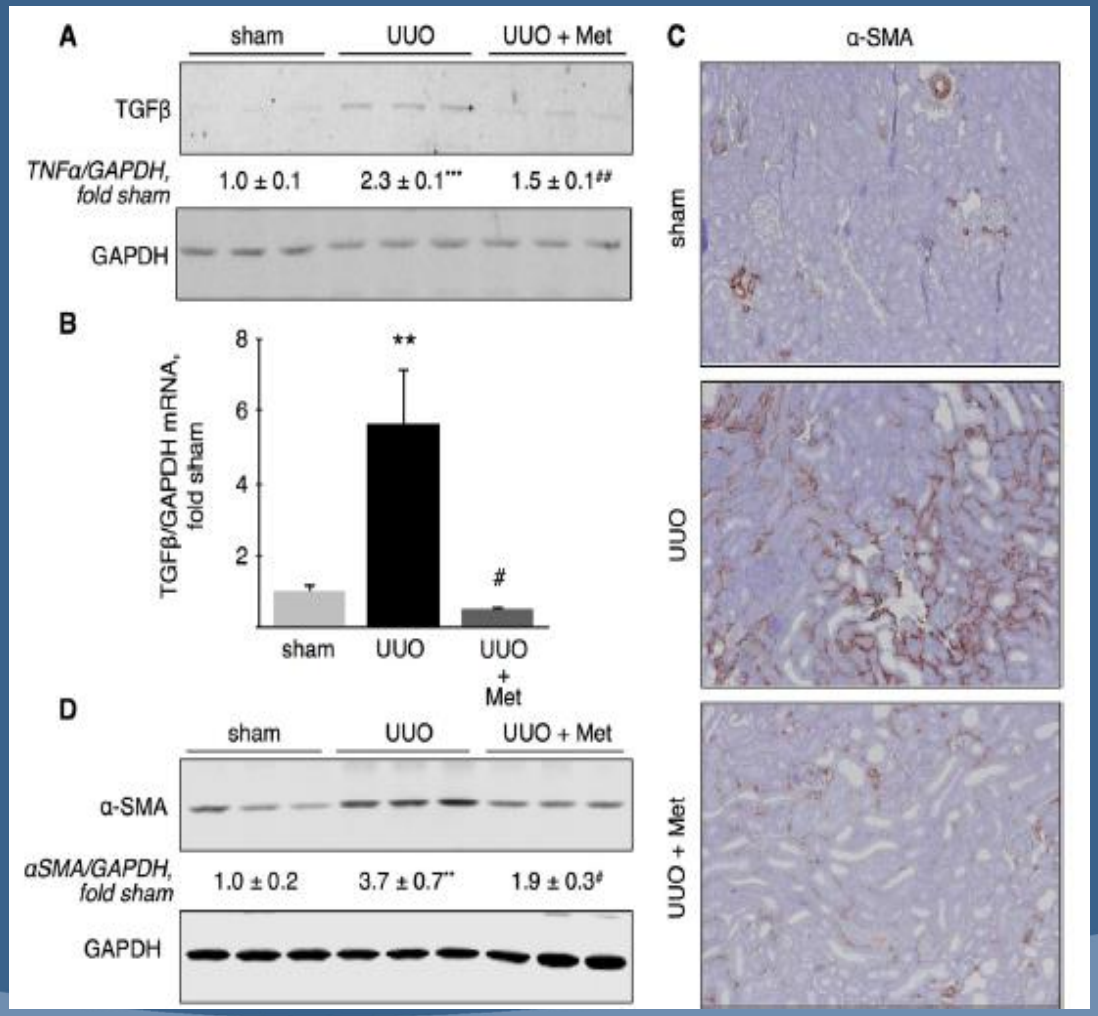
QO2/TNa ml/mmole: metabolic efficiency

Metformin prevents renal interstitial fibrosis in mice with unilateral ureteral obstruction



Cavaglieri R et al. Mol Cell Endoc 2015

Metformin prevents renal interstitial fibrosis in mice with unilateral ureteral obstruction



Our results show that metformin prevents or slows down the onset of renal inflammation and fibrosis in mice with UUO, an effect that could be mediated by activation of AMPK.

Metformin attenuates folic-acid induced renal fibrosis in mice: Metformin attenuates folic-acid induced renal fibrosis 2018 J Cel Phycsiology

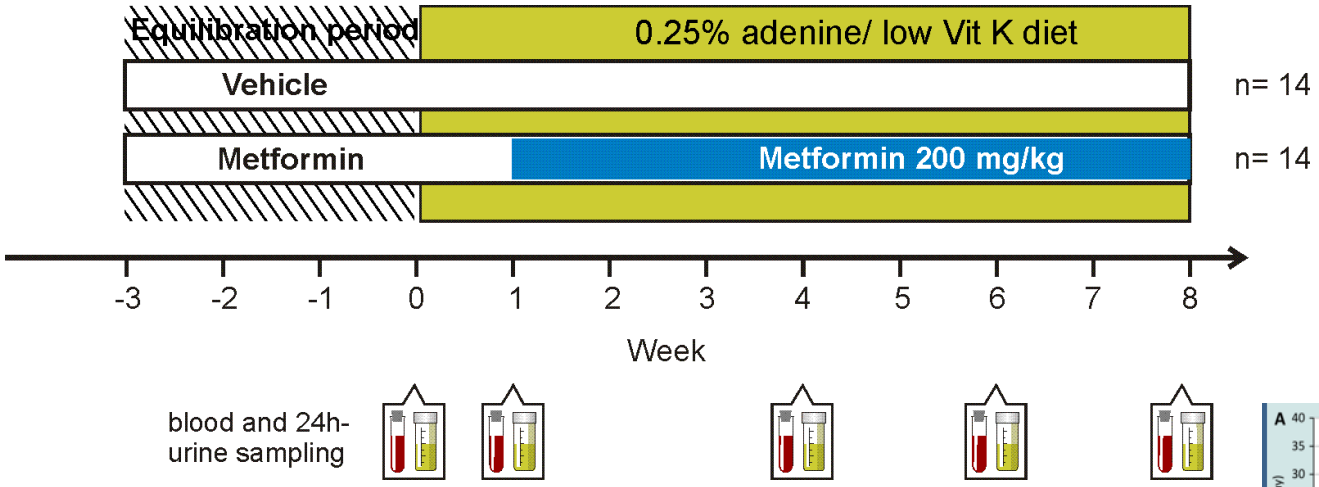
Cavaglieri R et al. Mol Cell Endoc 2015

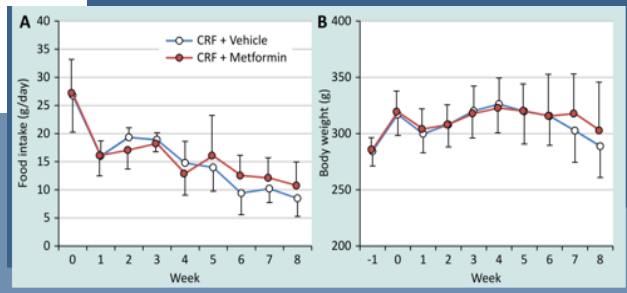
Metformin prevents the development of severe chronic kidney disease and its associated mineral and bone disorder

Kidn Intern 94; 102-113, 2018

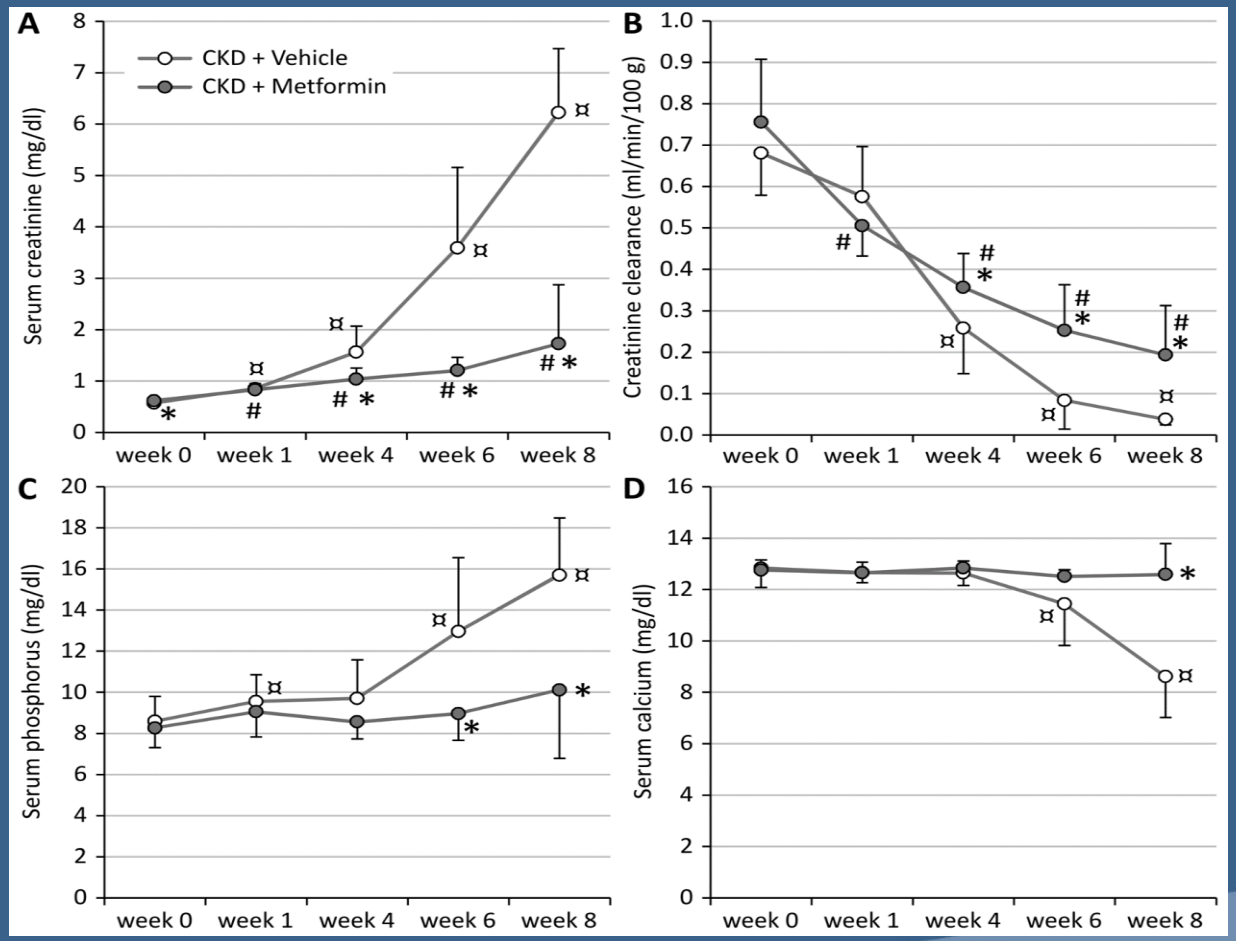
Ellen Neven[1], Benjamin Vervaet[1], Kerstin Brand[3], Ulrike Gottwald-Hostalek[3], Britt Opdebeeck[1], Annelies De Maré[1], Anja Verhulst[1], Jean-Daniel Lalau[2], Said Kamel[2], Marc E. De Broe[1] and Patrick C. D'Haese[1]

[1]Laboratory of Pathophysiology, Department of Biomedical Sciences, University of Antwerp, Antwerp, Belgium; [2]Unité Institut National de la Santé et de la Recherche Médicale U-1088, Université de Picardie Jules Verne, Amiens, France; and [3]Merck KGaA, Darmstadt, Germany



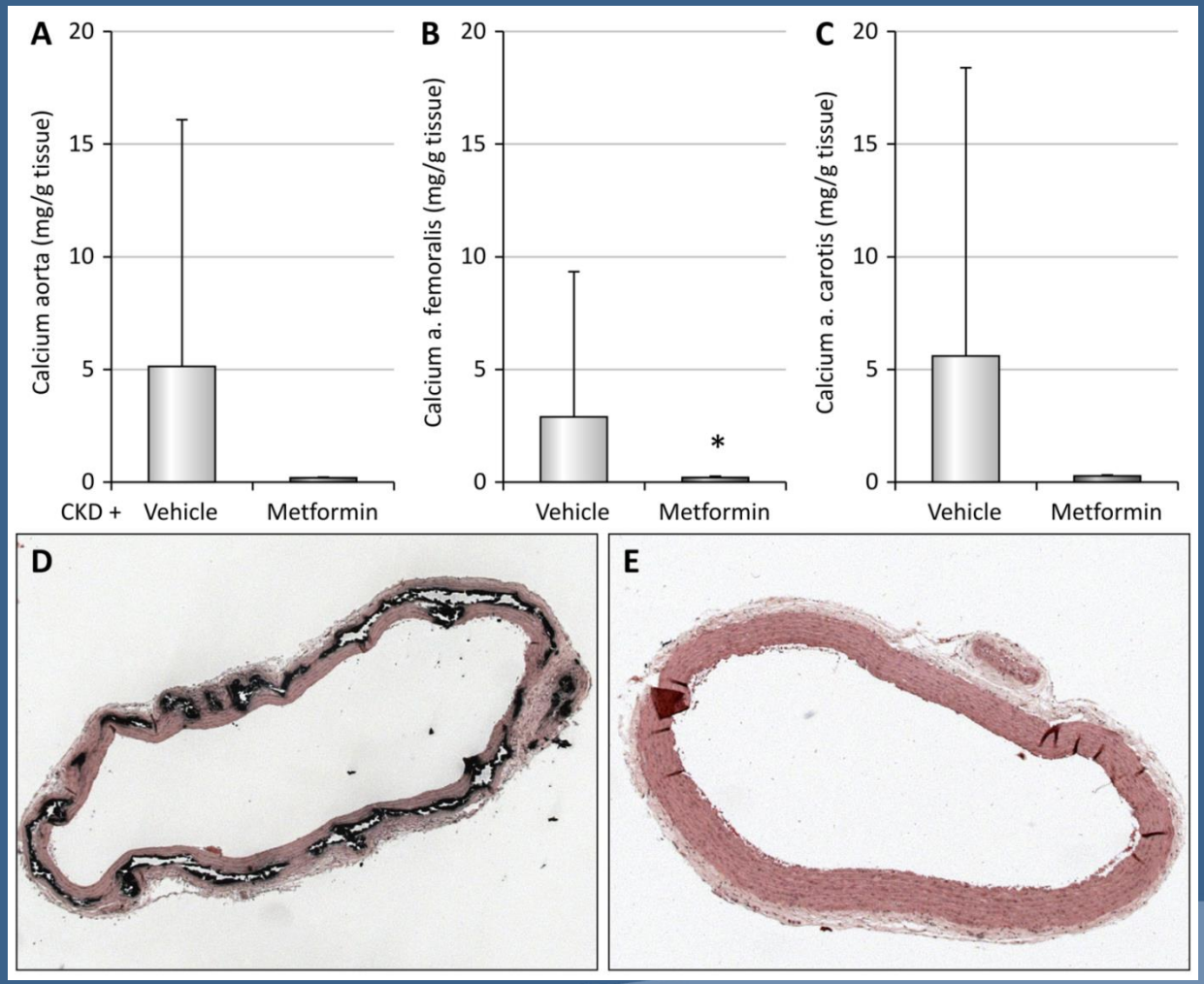


Results – renal function, Ca and P Adenine model



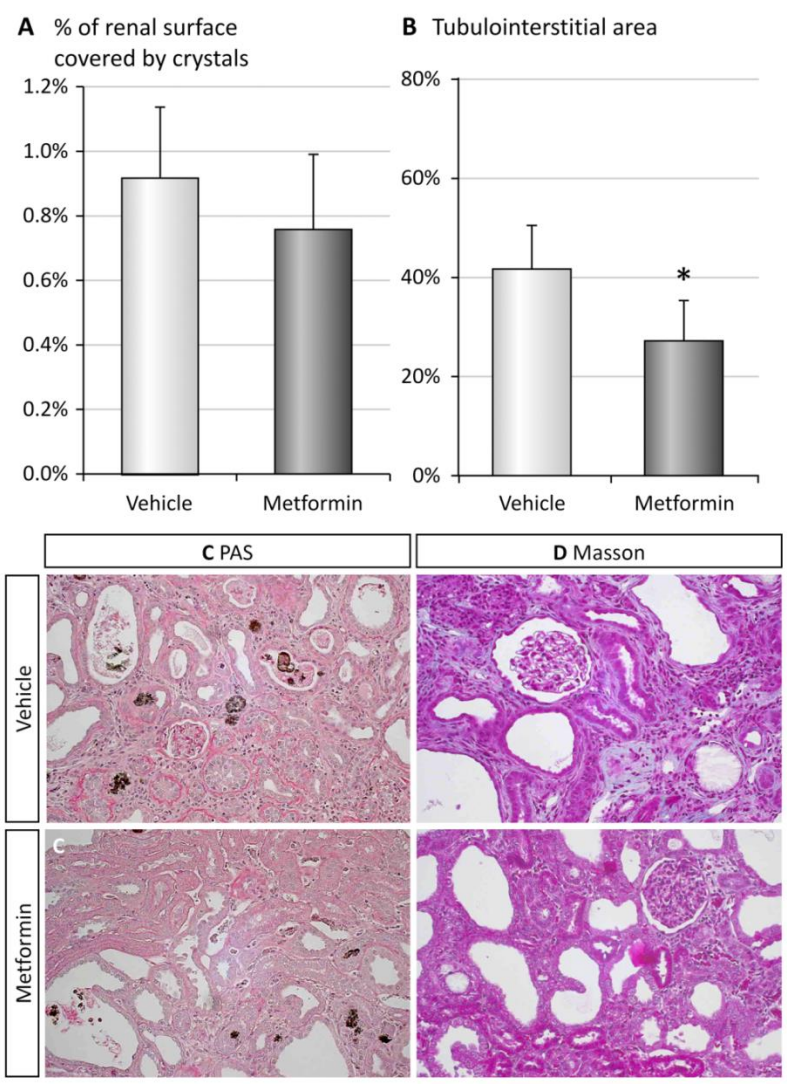
Neven E et al: Effect of metformin on vascular calcification in CKD rats

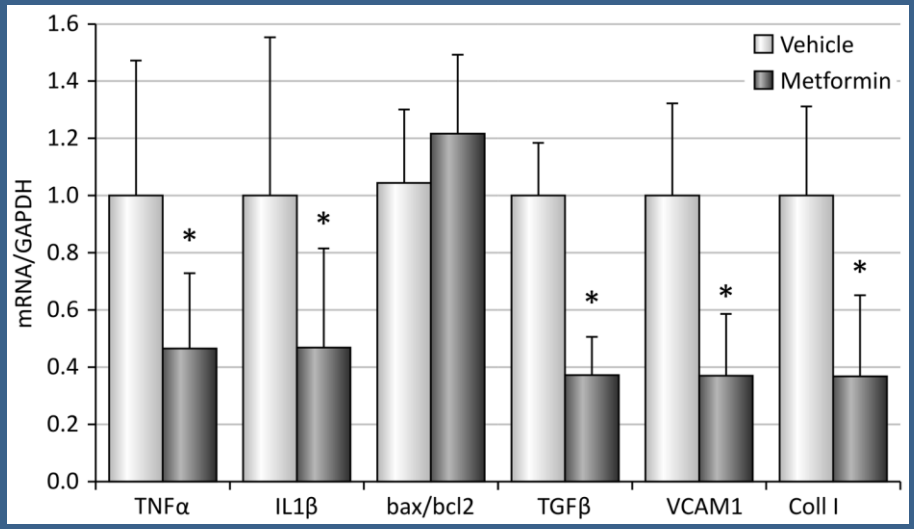
Results – arterial calcium



?

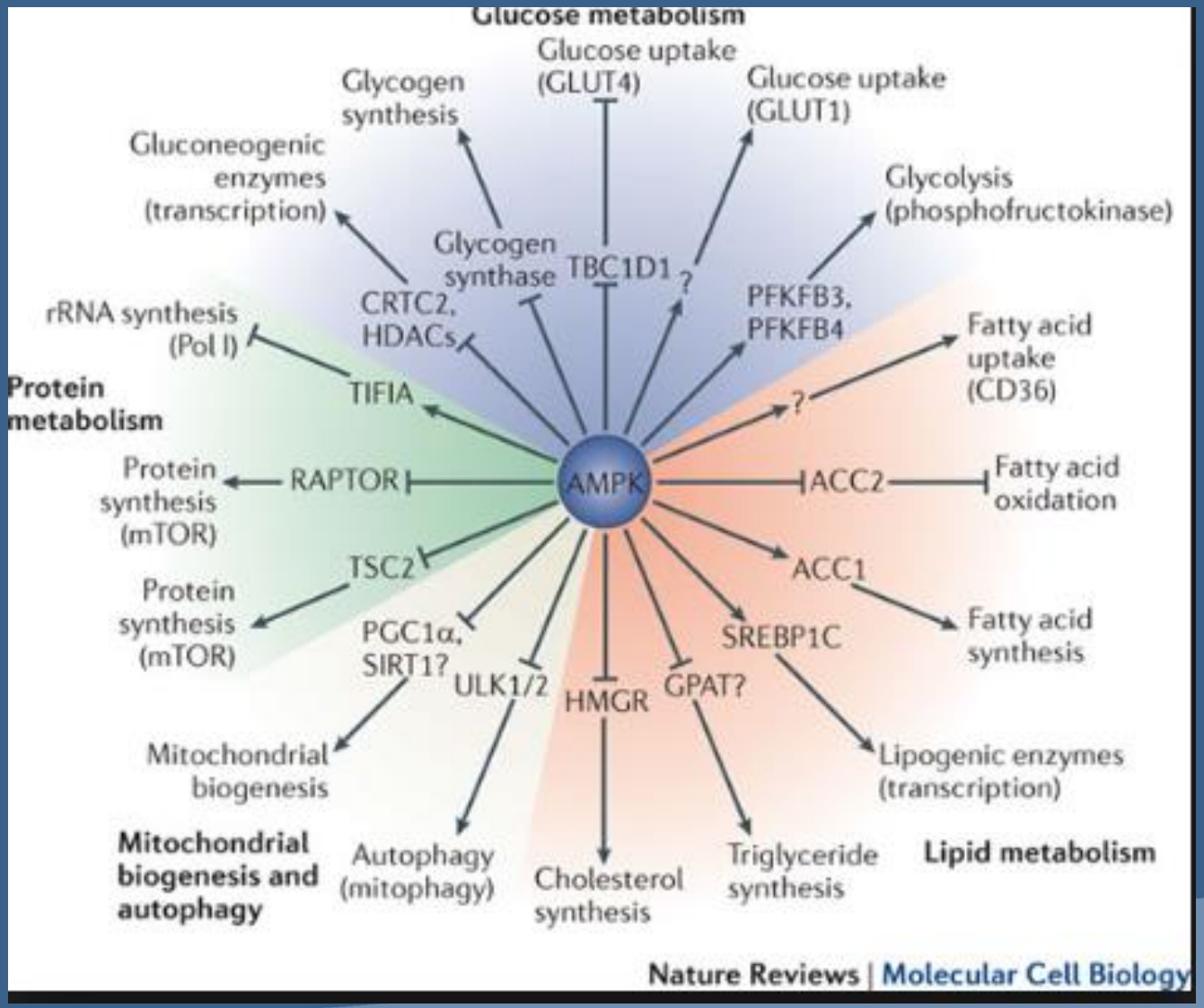
Results –





this animal model. Thus, metformin protected against the development of severe CKD and preserved calcium phosphorus homeostasis. As a result of its beneficial impact on renal function, associated comorbidities such as vascular calcification and high bone turnover disease were also prevented.

Neven E et al: Effect of metformin on vascular calcification in CKD rats



5' adenosine monophosphate-activated protein kinase

RENOPROTECTION of METFORMIN

- AMPK – beta 1 KO mouse Metformin remains renoprotective in UUO models

- Renoprotective action is independant of the expression of OCT1/2 as deemonstrated in OCT1/2 _/_ mouse
- OCT1/2 the most abundant isoform in the kidney

- Metformin enhances gluose uptake and acts renoprotective by reducing SHIP2 activity (lipid phosphatase, Src homology2 domain inositol phosphatase)
- SHIP2 suppresses insulin signaling by reducing Akt activation ---- insulin resistance (in press)

- Autophagic flux (autophagosomes) and fusion with lysosomes is crucial in cell survival. Metformin induces autophagy.
- The question of autophagy as renoprotector and which relevant pathways involved ??? R Corremans FWO fellowship 2018

Risk of acute kidney injury and survival in patients treated with Metformin: an observational cohort study

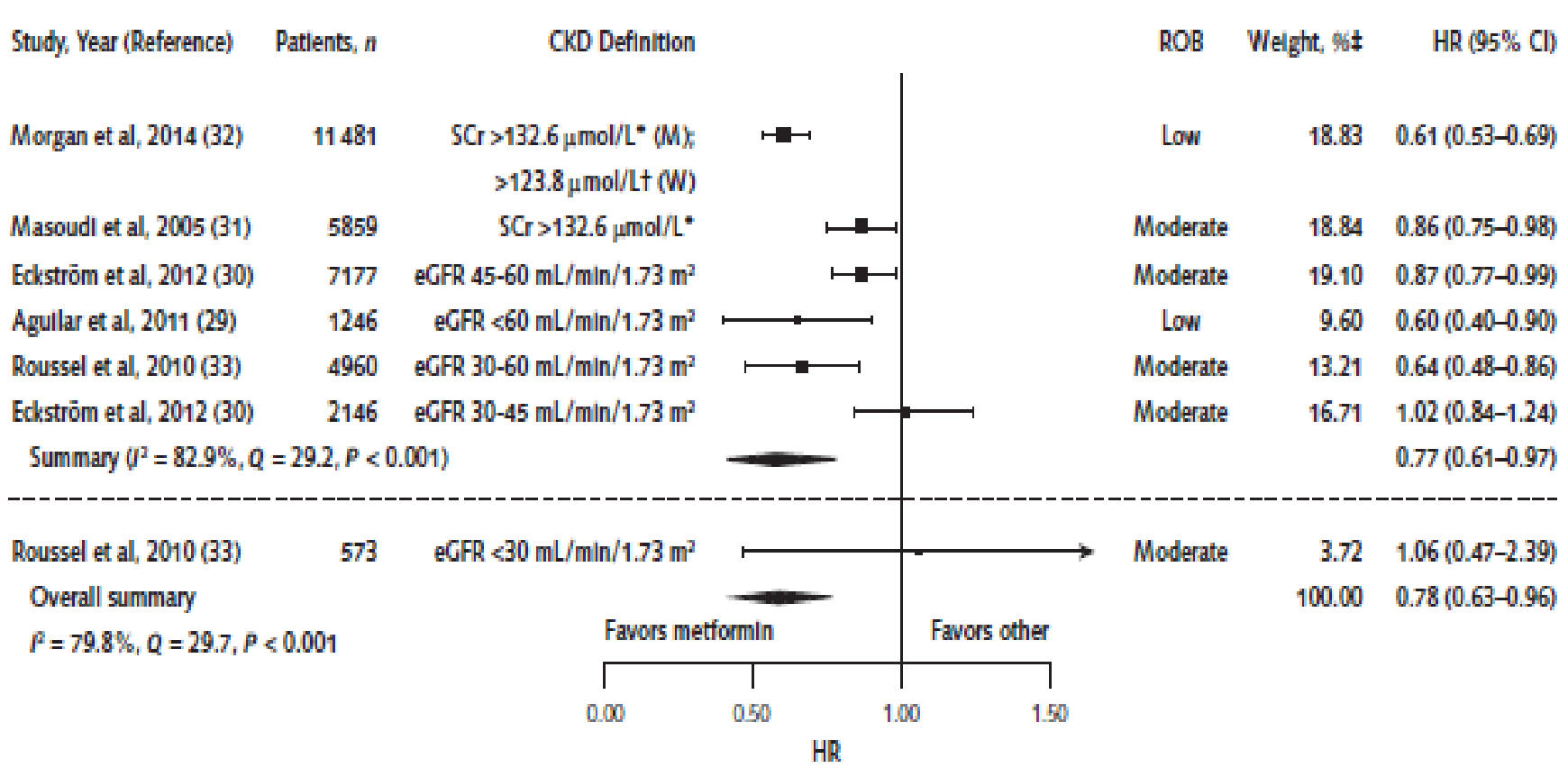
Samira Bell1et al BMJ Nephrology Oct 2017

Results: Twenty-five thousand one-hundred fourty-eight patients were included with a total person-time of 126,904 person years. 4944 (19.7%) people had at least one episode of AKI during the study period. There were 32.4 cases of first AKI/1000pyrs in current metformin exposed person-time periods compared to 44.9 cases/1000pyrs in unexposed periods. After adjustment for age, sex, diabetes duration, calendar time, number of diabetes drugs and baseline renal function, current metformin use was not associated with AKI incidence, HR 0.94 (95% CI 0.87, 1.02, p = 0.15). Among those with incident AKI, being on metformin at admission was associated with a higher rate of survival at 28 days (HR 0.81, 95% CI 0.69, 0.94, p = 0.006) even after adjustment for age, sex, pre-admission eGFR, HbA1c and diabetes duration.

Conclusion

Our large cohort of metformin users provides a reassuring message of the safety of metformin in patients with or without a background of CKD and supports the recent revision of FDA and EMA guidance on metformin prescribing in patients with renal impairment. We have also demonstrated that metformin does not adversely affect survival in patients with AKI.

Figure 2. Meta-analysis of all-cause mortality among patients with moderate to severe CKD receiving treatment regimens including metformin versus those receiving regimens without metformin.



Studies are listed according to increasing CKD severity. Eckström and colleagues (30) and Roussel and colleagues (33) stratified their respective populations by eGFR; these eGFR categories are presented separately for these studies. Summary data above the horizontal dashed line reflect a sensitivity analysis excluding 573 patients with an eGFR <30 mL/min/1.73 m². CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; HR = hazard ratio; M = men; ROB = risk of bias; SCr = serum creatinine; W = women.

* 1.5 mg/dL.

† 1.4 mg/dL.

‡ Numbers do not total 100% because of rounding.

Ann Intern Med 2016

??

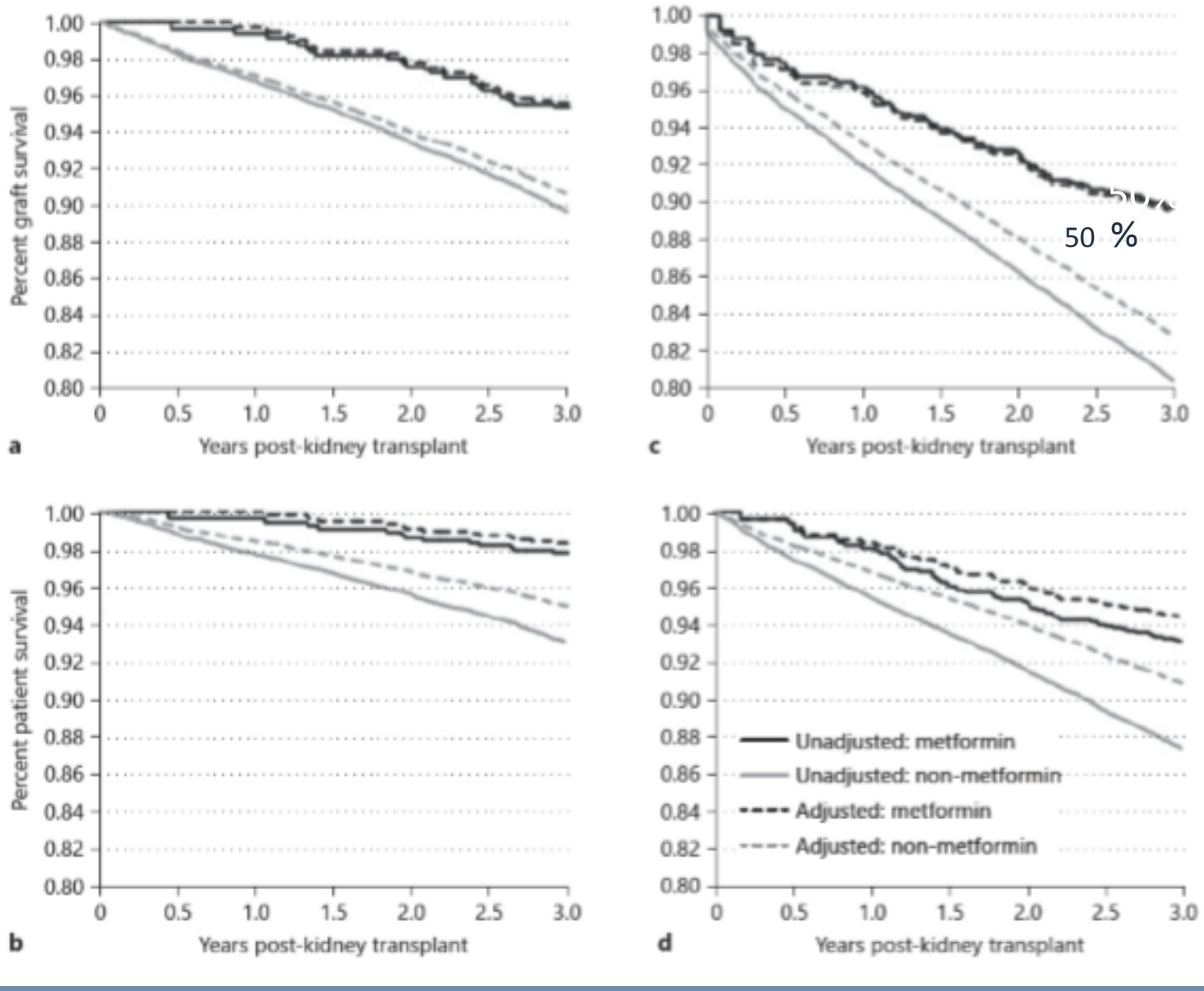
Metformin Use in Kidney Transplant Recipients in the United States: An Observational Study Am. J. Nephrol. 2014; 40; 546,
Jenise Stephen Teresa L. AndersonHaag Sally Gustafson Jon J. Snyder Bertram L. Kasiske Ajay K. Israni

- In this retrospective cohort study, we linked Scientific Registry of Transplant Recipients data for all incident kidney transplants 2001–2012 and national pharmacy claims (n = 46,914). We compared recipients having one or more pharmacy claims for a metformin containing product (n = 4,609) and recipients having one or more claims for a non-metformin glucose-lowering agent (n = 42,305)

- Despite metformin being contraindicated in renal dysfunction, many kidney transplant recipients receive it, and it is not associated with worse patient or allograft survival.

Living donor

Deceased donor



RenoMet

Metformin as RenoProtector in Non-Diabetic Patients with Progressive Chronic Kidney Disease (CKD stages 2, 3A and 3B):

a multi-centre, practice-oriented, repurposing, double-blind, placebo-controlled, randomized clinical trial

Laboratory of Pathophysiology
University of Antwerp

UNIVERSITAIR ZIEKENHUIS ANTWERPEN
UZA
kennis / ervaring / zorg

KCE
Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

Primary Objective

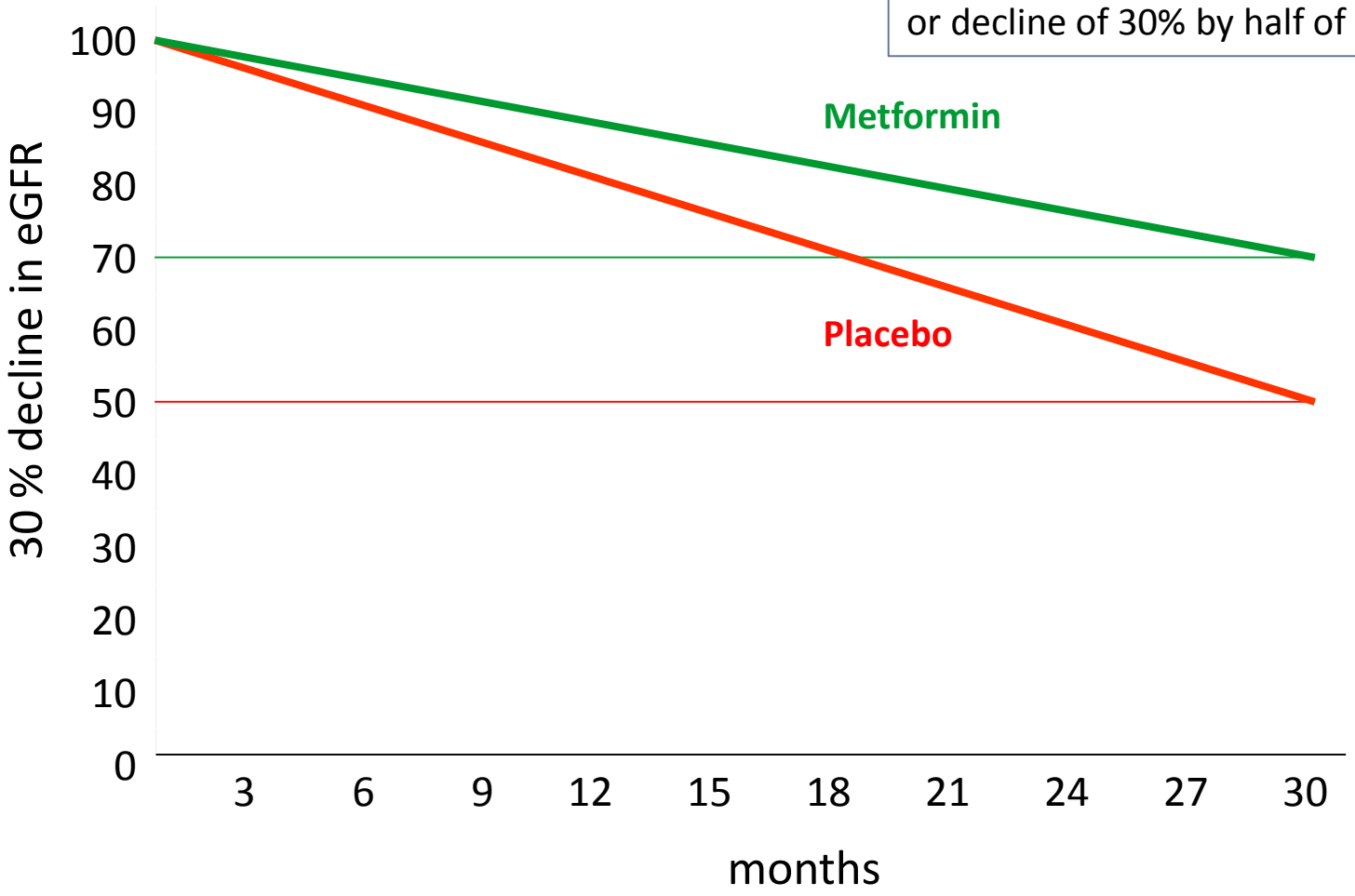
to demonstrate that a Metformin dose of 1000 mg/day,
can effectively and safely slow the progression of renal failure
in non-diabetic patients with chronic renal failure
stages CKD 2, CKD3A and 3B

Survival analysis based on the time to event of reaching
a 30% decline of eGFR over the investigation period of 30 months
in the intervention group compared to the control group

Hazard ratio based on the number of patients reaching
a 30% decline of eGFR over the investigation period of 30 months
in the intervention group compared to the control group

Primary Endpoint

Mean eGFR at start: 50 ml/min
Mean decline: 6 ml/min/year
Decline after 30 months: 15 ml/min
or decline of 30% by half of the patients



Secondary Endpoints

- Incidence of mortality, development of end-stage renal disease, specific co-morbidities and hospitalization
- Evolution of the renal function
- Quality of life
- Adverse drug reactions
- Lactic acidosis

Trial participants

- Patients will be recruited in 12 centers
  (5 in Flanders, 5 in Wallonia , 2 Brussels)
- Inclusion:
  - Adult patients (18-75y), both gender
  - eGFR between 30-90 ml/min/1,73m²
  - Proteinuria < 3,5 gr/24hrs
  - Decline of eGFR between 2,0 and 15,0 ml/min/year
- Exclusion:
  - Illiteracy, language problems, mental deterioration
  - Clinical problems: Diabetes, COPD, Congestive heart failure, IBD, Stoma, Tx, Cirrhosis, Pregnancy
  - Confirmed elevated lactate level > 3,0 mmol/L

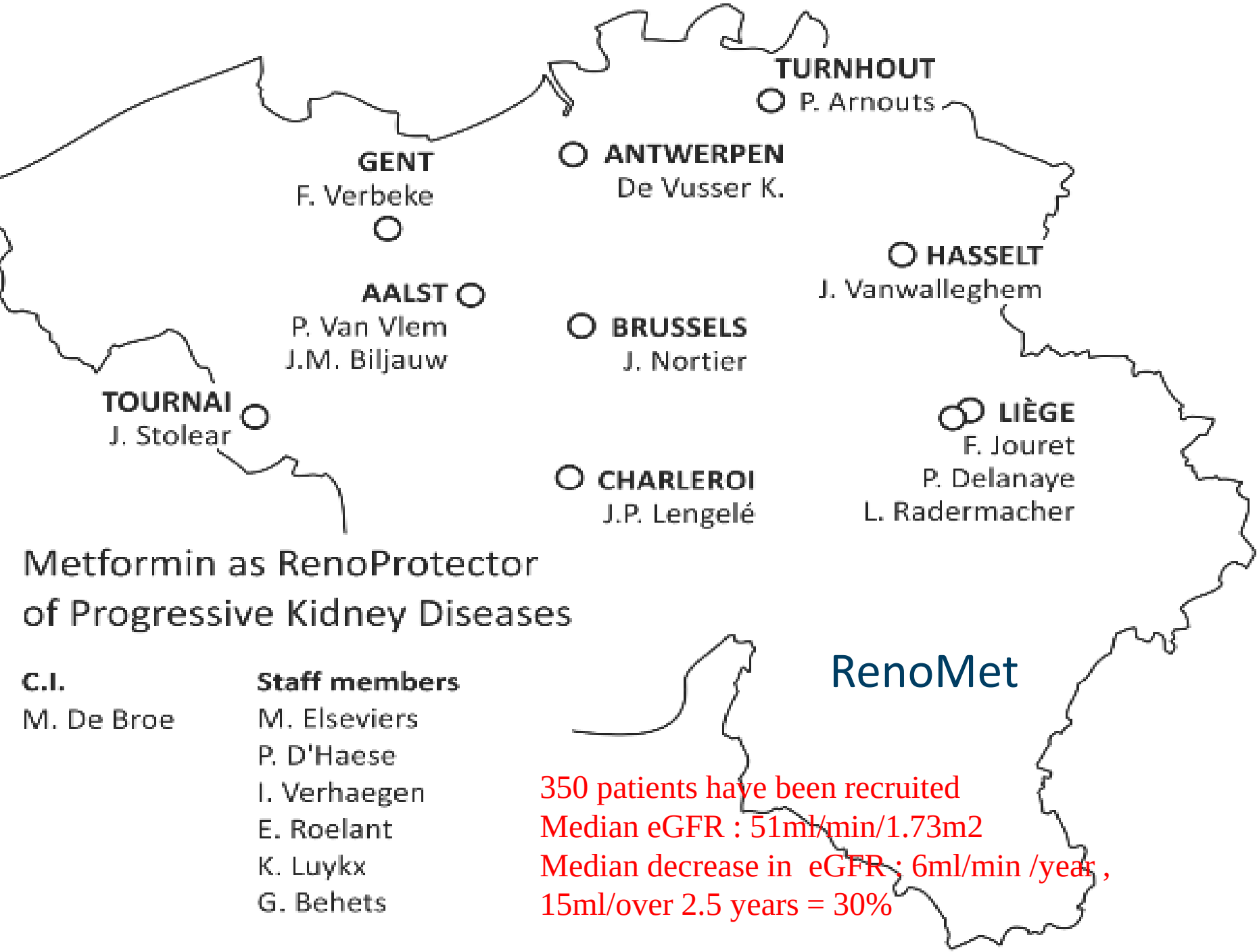
Intervention

Repurposing, double-blind, placebo-controlled, randomized clinical trial

- Treatment during 30 months
- Intervention group:
  Metformin slow release 1000 mg/day (2x500 mg) during evening meal
  (start-up: first month 500 mg)
- Control group:
  Matched placebo

SAMPLE SIZE

- With the treatment of Metformin, we hypothesize that after 2.5 years the hazard on the event will be 40% lower in the Metformin group compared to the standard care group corresponding to a hazard ratio of 0.60 (KeyRef 10)
- With an equal allocation to treatment and control group, a power of 80% and a two sided 5.0 % significance level the total number of events needed to obtain significant results will be 88. We expect a 10% censoring rate during the study period
- The total corresponding sample size will be 383 (191 in intervention group, 192 in control group). This sample size is calculated using a web-based calculator (http://www.sample-size.net/sample-size-survival-analysis/), a baseline event rate (events/unit time) for group 0 = 0.500 (BER0) and a planned average length of follow-up (FU) = 1.00.



Metformin as RenoProtector of Progressive Kidney Diseases

C.I.
M. De Broe

Staff members
M. Elseviers
P. D'Haese
I. Verhaegen
E. Roelant
K. Luykx
G. Behets

RenoMet

350 patients have been recruited
Median eGFR : 51ml/min/1.73m2
Median decrease in eGFR : 6ml/min /year ,
15ml/over 2.5 years = 30%

Adverse Effects of metformin in type 2 diabetes and CKD

Adverse effect	Frequency	Comments
Gastro-intestinal	Common	Usually mild and transient Reversible after dose reduction or drug discontinuation Metallic taste, anorexia, soft stools/diarrhea, nausea, vomiting, flatulence
Neurologic	Rare to moderate	Headache (6%), chills, lightheadedness, myalgia, weakness, altered metal status
Lactic acidosis	Very rare	Typically in the context of AKI, CKD and/or metformin overdose High fatality in case series
Hypoglycemia	Rare	More common with kidney dysfunction
Vitamin B12 deficiency	Rare	Metformin reduces intestinal absorption of vitamin B12 in up to 30% of patients and lowers serum B12 level in 5-10% of patients Rarely causes megaloblastic anemia

Metformin treatment in CKD Patients

- eGFR should be assessed every 6 months in CKD stage 3 (3A + 3B) and every 3 months in CKD 4
- Metformin dose should be further adjusted in case of CKD change and stopped in CKD5 patients
- Metformin therapy should be stopped in patients susceptible to experience acute kidney injury in the context of severe pathology such as sepsis, haemorrhage, vascular shock, etc...

Lactate and $HC0_3$- concentration

- Lactate and $HC0_3$- concentration should be assessed before introducing metformin
  - Metformin should not be started in patients with a baseline value > 2.5 mmol/L
  - control a baseline value > 1.5 mmol/L within the first month
- Lactate - HC03 monitored every 3 months , 1 year metformin treatment
  - a value > 2.5 mmol/L to be controlled within one month
  - a value > 5 mmol/L arrest of metformin
  - two consecutive values > 2.5 mmol/L arrest of metformin
- In the absence of high lactate the first year, lactate $HC0_3$ levels should be considered in case of intercurrent diseases, capable to generate lactic acidosis, acute kidney injury, sepsis, haemorrhage, vascular shock …

Conclusions

- Metformin was and still is an important drug in the treatment of diabetes type 2
- The use of Metformin in renal failure patients is more and more acceptable but never without risk: congestive heart failure, sepsis, acute renal failure, acute on chronic renal failure, liver insufficiency, pulmonary infectious diseases, dehydration, (plasma volume) ... change dramatically the PK of the drug. Clinical alertness
- Stop before or at the time of intravenous or intra-arterial iodinated contrast procedures. Control eGFR after procedures
- A comprehensive dose finding, tolerance, and pharmacokinetic study of Metformin in CKD 3A, 3B and 4 allows the use of Metformin in these patients provided the doses are adapted to the degree of CKD (CKD3A 1500mg/day, CKD3B 1000mg/day, CKD4 500mg /day)
- CKD5 remains a contraindication because of instability of the clinical situation

Most of the studies presented were conducted with financial and drug support by Merck KGaA, Darmstadt unrestrictive grant

METFORMIN in CKD Patients

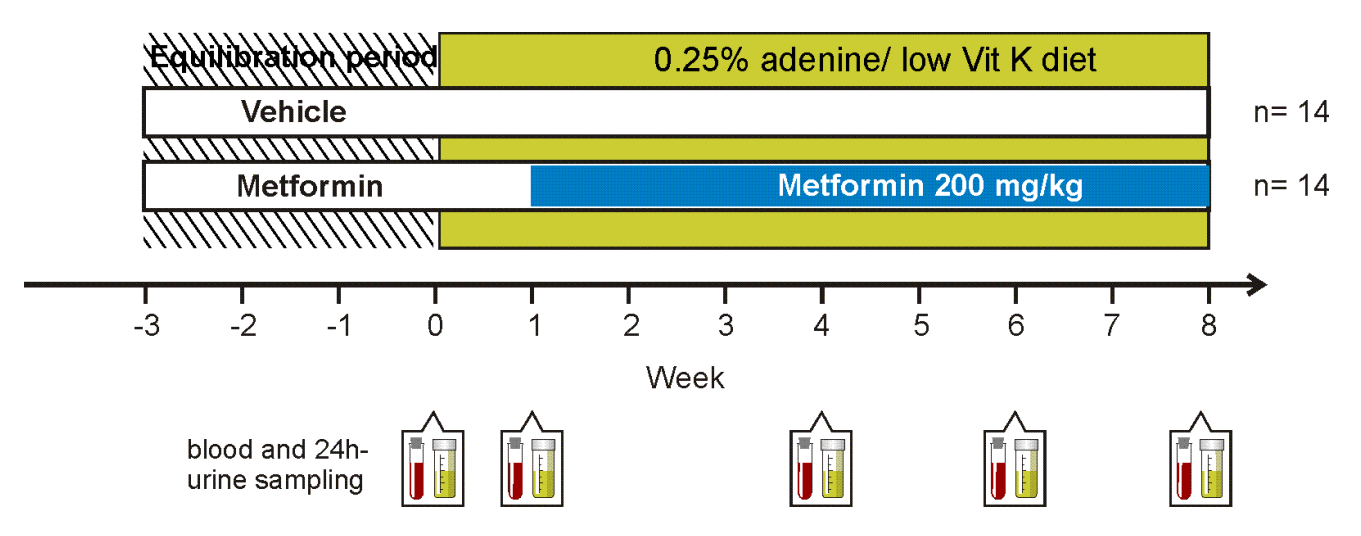
Not without risk ,clinical alertness

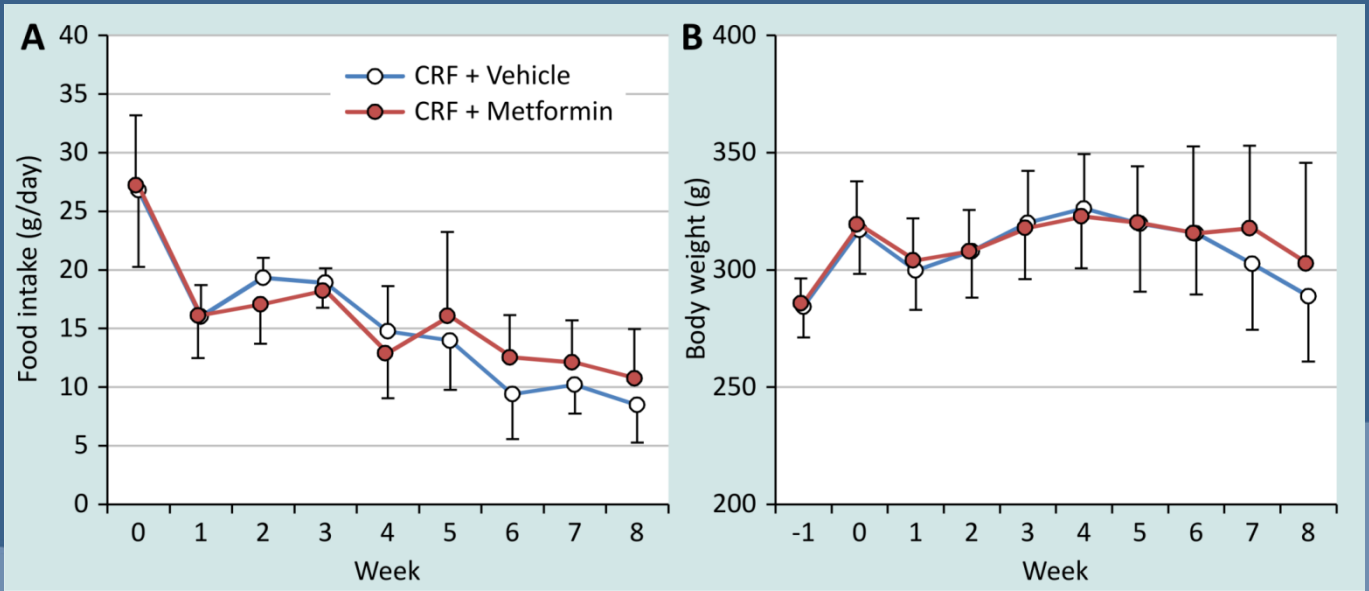
eGFR monitoring

Lactate and HC03 levels

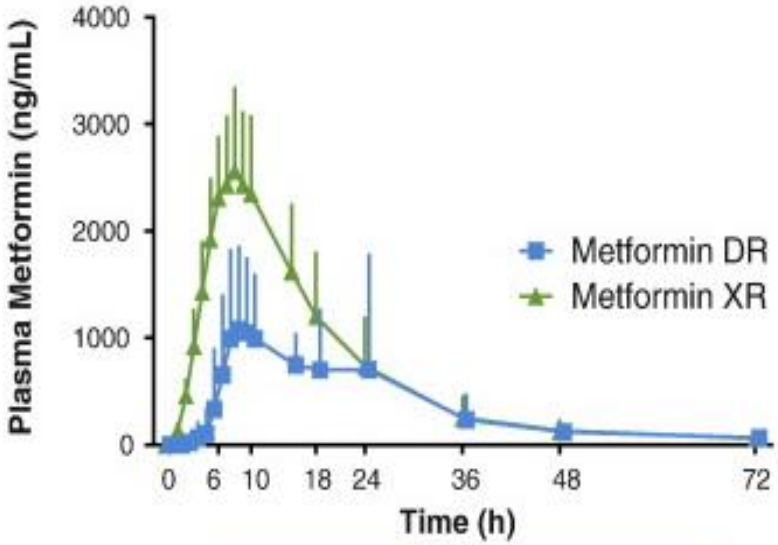
Renoprotection

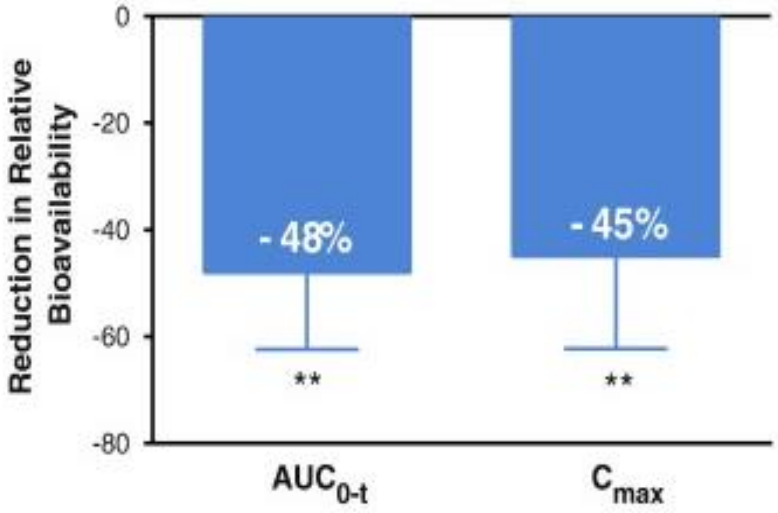
Ceçi n’est pas une abeille La Pautinie lente 2017

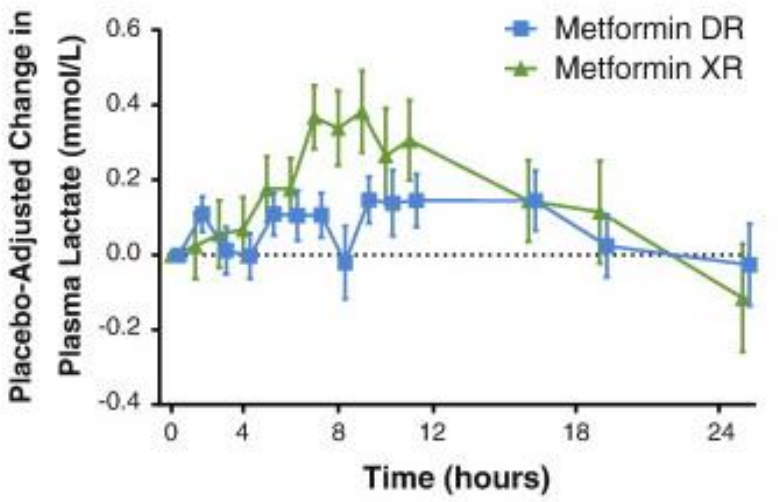


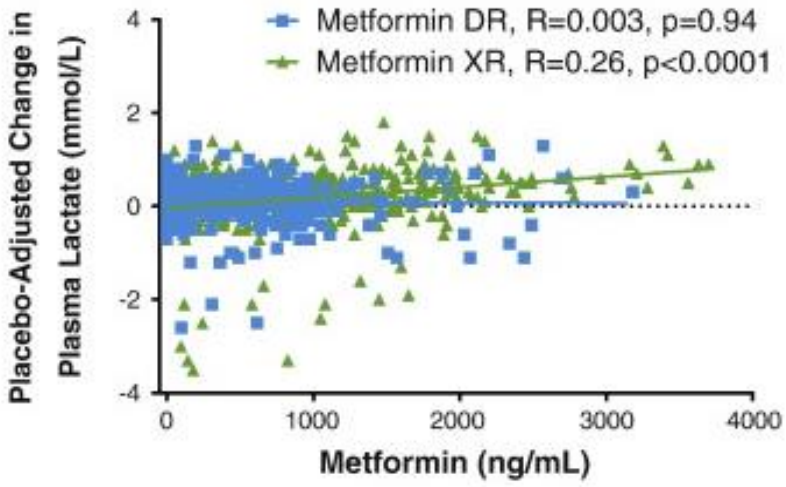


Neven E et al: Effect of metformin on vascular calcification in CKD rats (submitted)







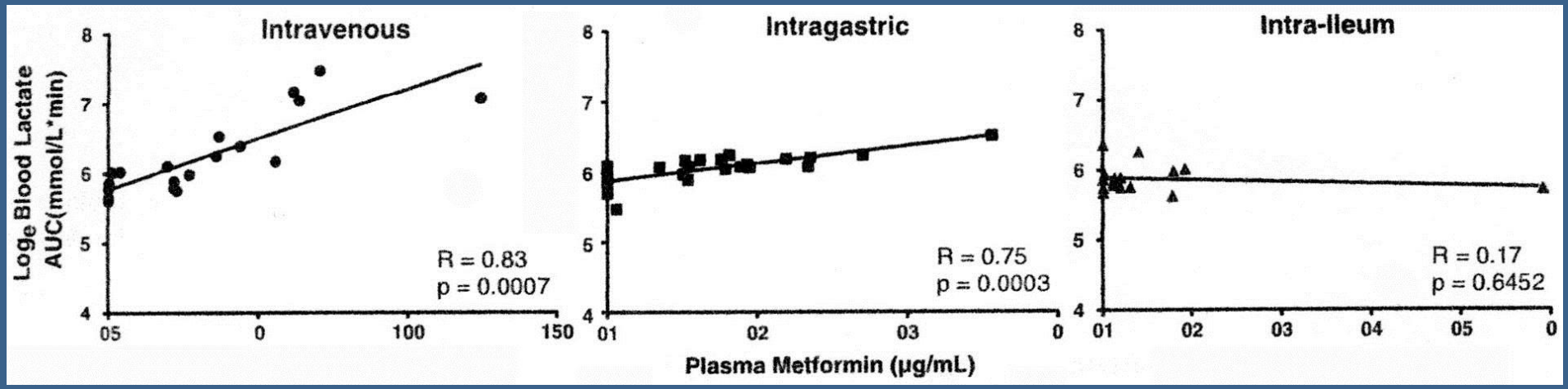


Metformin levels

Lactate levels

DeFronzo et al: Metabolism 65, 20, 2016

Blood lactic acid vs. plasma metformin



DeFronzo et al: Metabolism 65, 20, 2016

RENOMET 2018-2021

- Adult patients (18-75 years) of both gender, with chronic kidney disease (CKD stage 2, 3A or 3B, i. e. with estimated glomerular filtration rate (eGFR) between 30 and 90 ml/min/1.73m2), without and with proteinuria (below 3.5 g/24hrs) and showing a decline of eGFR between 2.0 and 15 ml/min/year are eligible for inclusion.
- Patients will be recruited in one of the ten participating renal care clinics (5 in Flanders, 5 in Wallonia) where they have regular follow-up visits for their chronic renal failure. CKD patients with diabetes will be excluded.
- Also CKD patients with overt proteinuria (more than 3.5 g/24hrs) and patients showing a fast decline of renal function (more than 15 ml/min/year during the preceding two years) will be excluded

450 patients have been recruited
Median eGFR : 51ml/min/1.73m2
Median decrease in eGFR : 6ml/min /year , 15ml/over 2.5 years = 30%

RenoMet study: visit schedule

	Month (-/+ 2 weeks)	Routine Investigations	Extra Investigations
Baseline visit	0	+	Procedure of Informed Consent Baseline data collection (demo-graphics, comorbidities, medication), Samples (1) + Qol (4) + mGFR (5)
FU visit 1	2	+	Samples (1) + Compliance (2) + Adverse events (3) + Qol (4)
FU visit 2	6	+	idem
FU visit 3	10	+	idem
FU visit 4	14	+	idem
FU visit 5	18	+	idem
FU visit 6	22	+	idem
FU visit 7	26	+	idem
FU visit 8	30	+	Idem + mGFR (5)

Routine investigation: clinical investigation, routine blood and urine determinations, serum lactate and bicarbonate concentration

Extra investigations: (1) extra blood and urine sample for central determination of serum creatinine and proteinuria; **(2)** assessment of compliance using MEMS devices; **(3)** assessment of adverse events; **(4)** quality of life assessment; **(5)** extra blood sample for mGFR determination (if in protocol)