BALANCING RISK AND BENEFIT IN CHRONIC KIDNEY DISEASE ?

(metformin, sulfonylureas, insulin)

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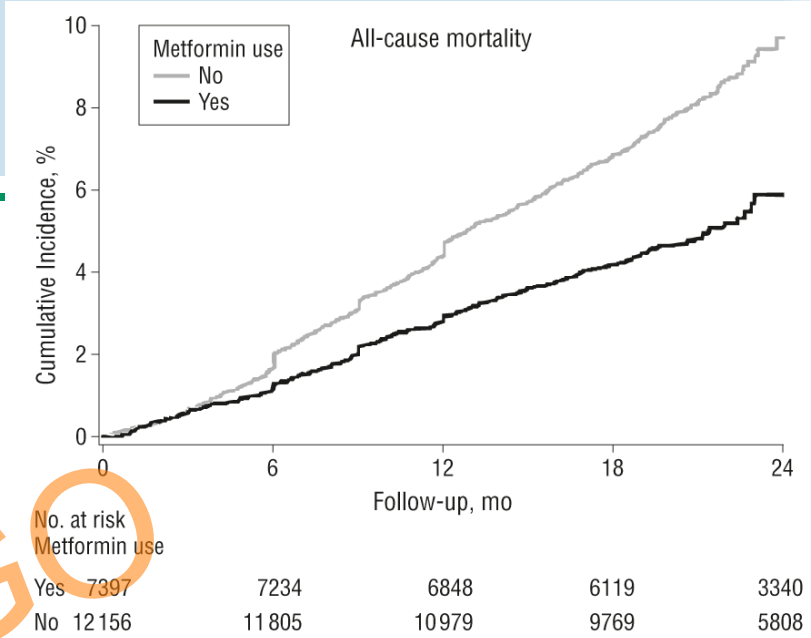
Disclosure of Interests

MCT has received honoraria for educational symposia and expert panels provided on behalf of:

Astra-Zeneca, Abbott, Reata, Abvie, Sanofi Aventis, BMS, Boehringer Ingelhiem, Lilly, MSD, Servier, Janssen-Cilag, Amgen & Allergan

METFORMIN in CKD

- ☑ CHEAP
- ☑ EFFICACY
- ☑ ↓HYPOGLYCAEMIA
- ☑ ↓WEIGHT GAIN
- ☑ ↓ MORTALITY ↓ CANCER (?)

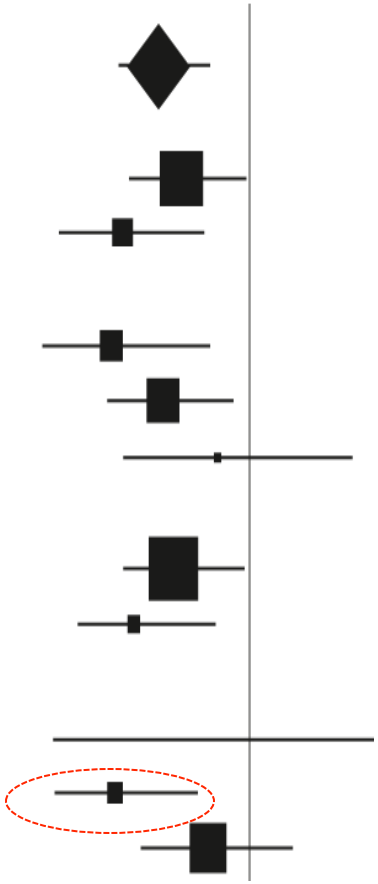


- ☒ ACCUMULATION/ADJUSTMENT
- ☒ ↑ GASTRO-INTESTINAL TOXICITY
- ☒ ↑LACTATE (ACIDOSIS?)
- ☒ ↓VITAMIN B12?

METFORMIN & MORTALITY in CKD

Arch Intern Med. 2010;170(21):1892-1899

	Metformin Use		Adjusted HR		*P* Value for
	Yes	No	(95% CI)	*P* Value	Interaction
Overall Population	341/7397	929/12 156	0.76 (0.65-0.89)	<.001	
Sex					
Male	243/4845	617/7954	0.82 (0.68-0.99)	.04	.07
Female	98/2548	312/4195	0.66 (0.49-0.88)	.005	
Age, y					
40-65	78/2987	176/3859	0.63 (0.45-0.89)	.008	.07
>65-80	191/3791	532/6768	0.77 (0.62-0.95)	.02	
>80	71/598	220/1492	0.92 (0.66-1.28)	.61	
CHF					
No	221/6002	488/9120	0.80 (0.66-0.98)	.03	.39
Yes	116/1220	419/2790	0.69 (0.54-0.90)	.006	
eGFR, mL/min/1.73 m^2					
0-<30	14/118	90/455	1.06 (0.47-2.38)	.89	.13
30-<60	86/1572	336/3388	0.64 (0.48-0.86)	.003	
≤60	188/4442	379/6326	0.89 (0.71-1.11)	.30	



* adjusted for propensity score

METFORMIN in CKD

- ☑ CHEAP
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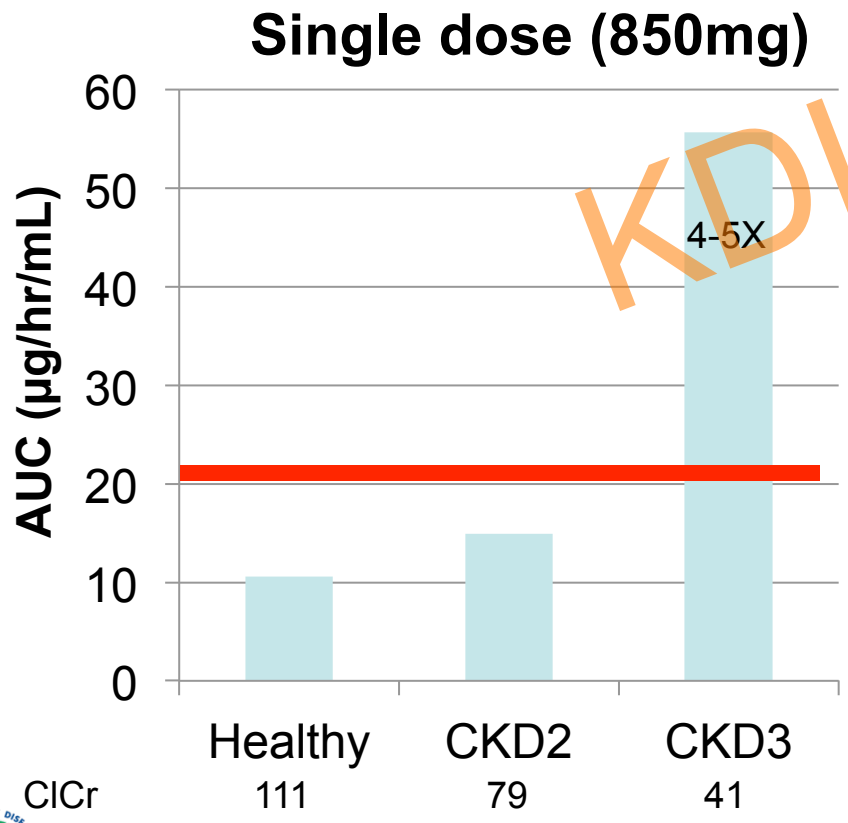
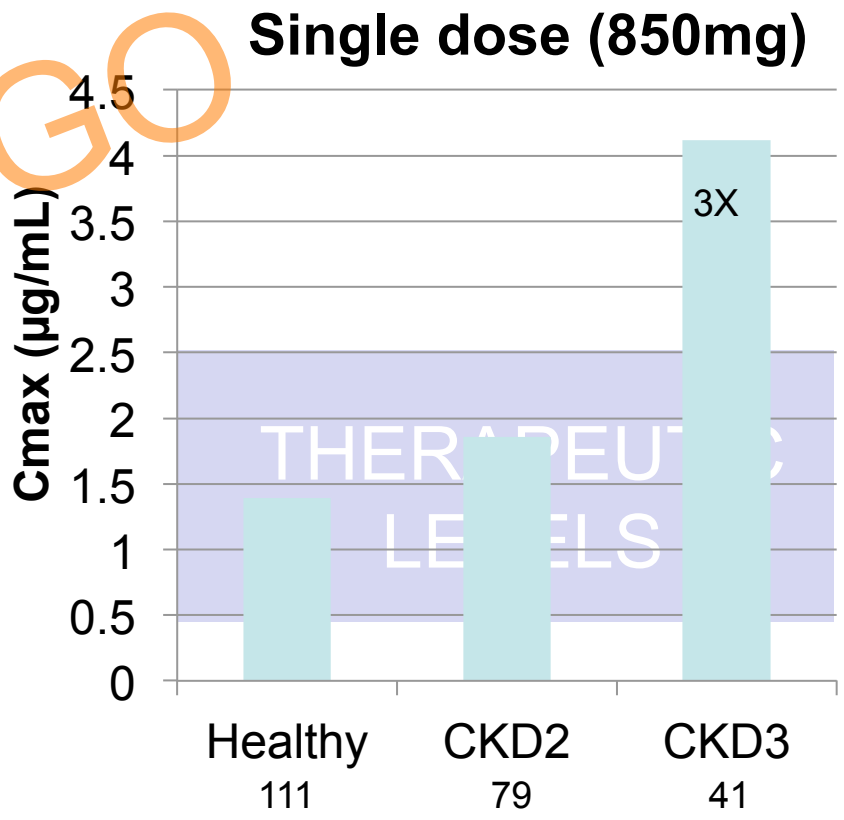
- ☒ ↑LACTATE (ACIDOSIS?)
- ☒ ↓VITAMIN B12 (~↓20%/3 years)

METFORMIN pharmacokinetics

J Clin Pharmacol. 1995;35(11):1094-1102

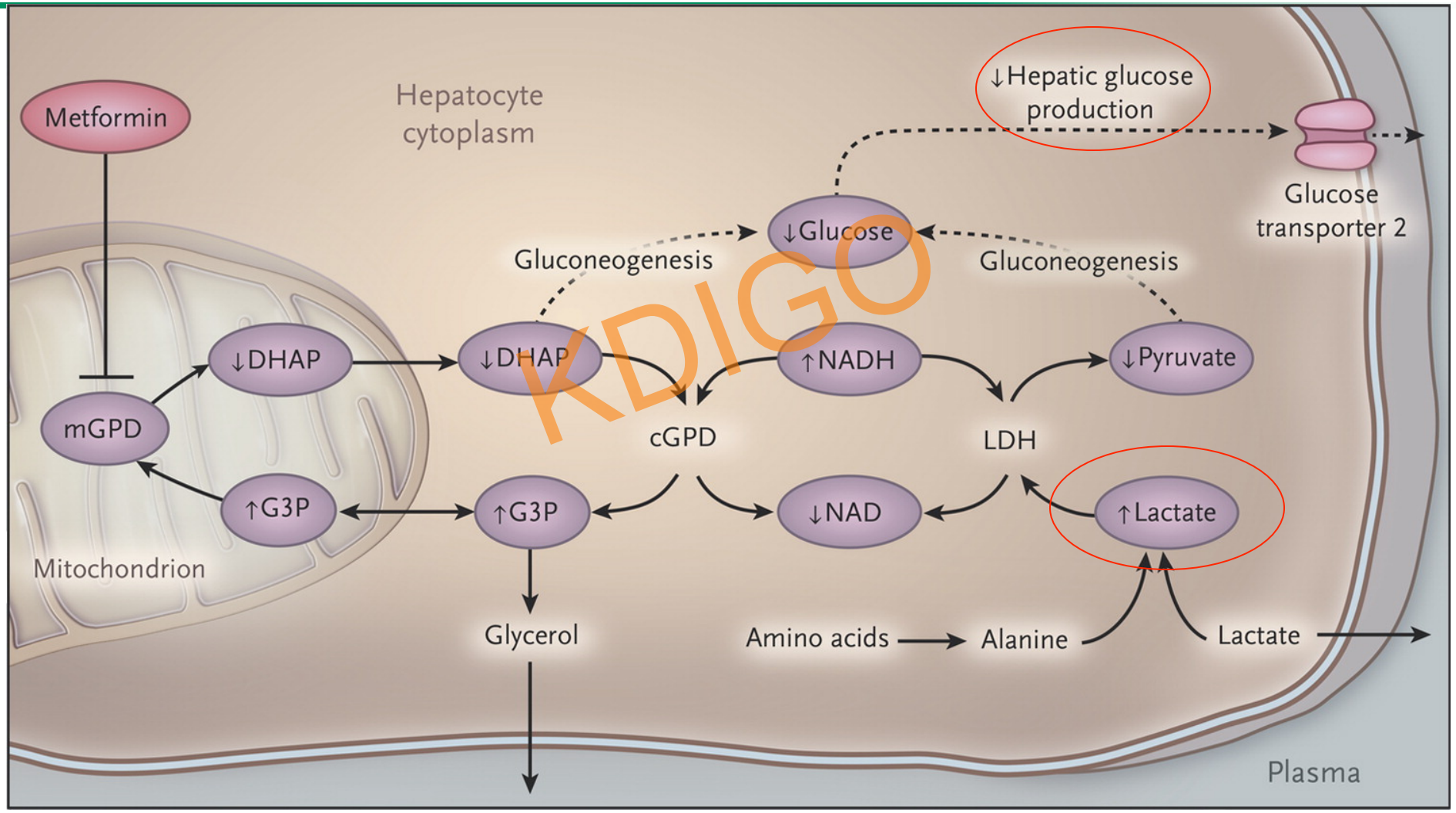
If a drug is eliminated primarily through renal excretory mechanisms, impaired renal function usually alters the drug's PK to an extent that the dosage regimen needs to be changed from that used in patients with normal renal function.





METFORMIN and LACTATE

Ferrannini E. N Engl J Med 2014;371:1547-1548.

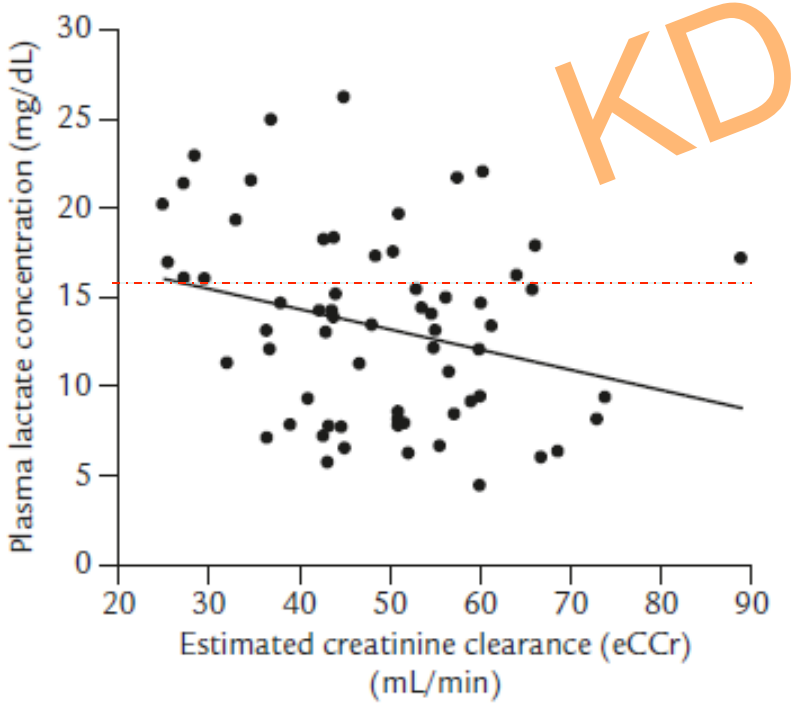


METFORMIN and LACTATE

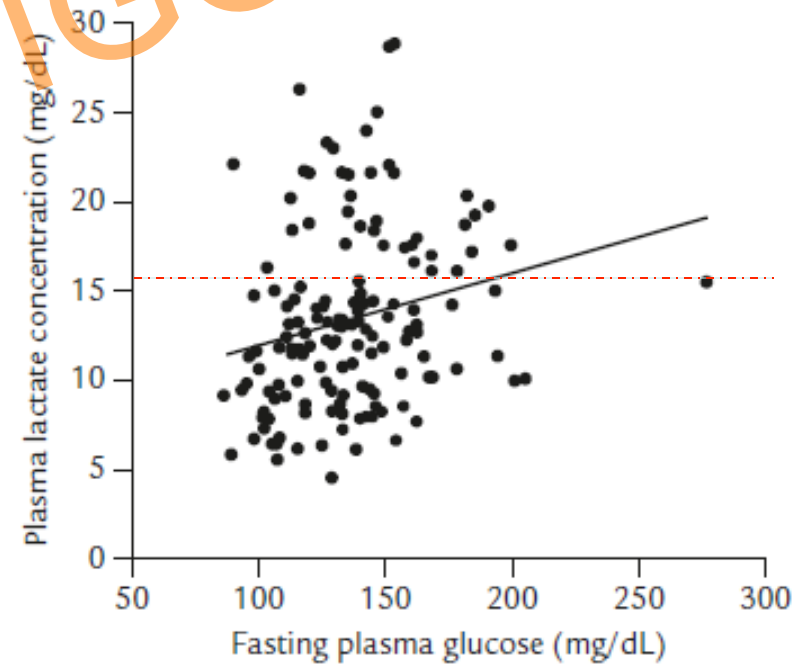
J Chin Med Assoc (2010)

Circulating lactate levels among metformin-treated patients are modestly higher compared with those taking other agents (1.32 vs 1.14 mmol/L),), Elevated lactate concentrations (>2.0 mmol/L) were nearly 3 times more common in metformin-treated patients (9.2% vs 3.8%, *P* < .001).
Not related to dose of drug levels?

Renal function



Glycaemic control



METFORMIN in CKD

Better the devil you know?

Table 2. Possible Approach to Metformin Prescribing in the Setting of CKD[a]

CKD Stage	eGFR, mL/min per 1.73 m^2	Maximal Total Daily Dose, mg	Other Recommendations
1	≥90	2550	
2	60 -<90	2550	
3A	45 -<60	2000	Avoid if kidney function is or expected to become unstable Consider more cautious follow-up of kidney function
3B	30 -<45	1000	Do not initiate therapy at this stage but drug may be continued Avoid if kidney function is or expected to become unstable Consider more cautious follow-up of kidney function
4	15 -<30	Do not use	
5	<15	Do not use	

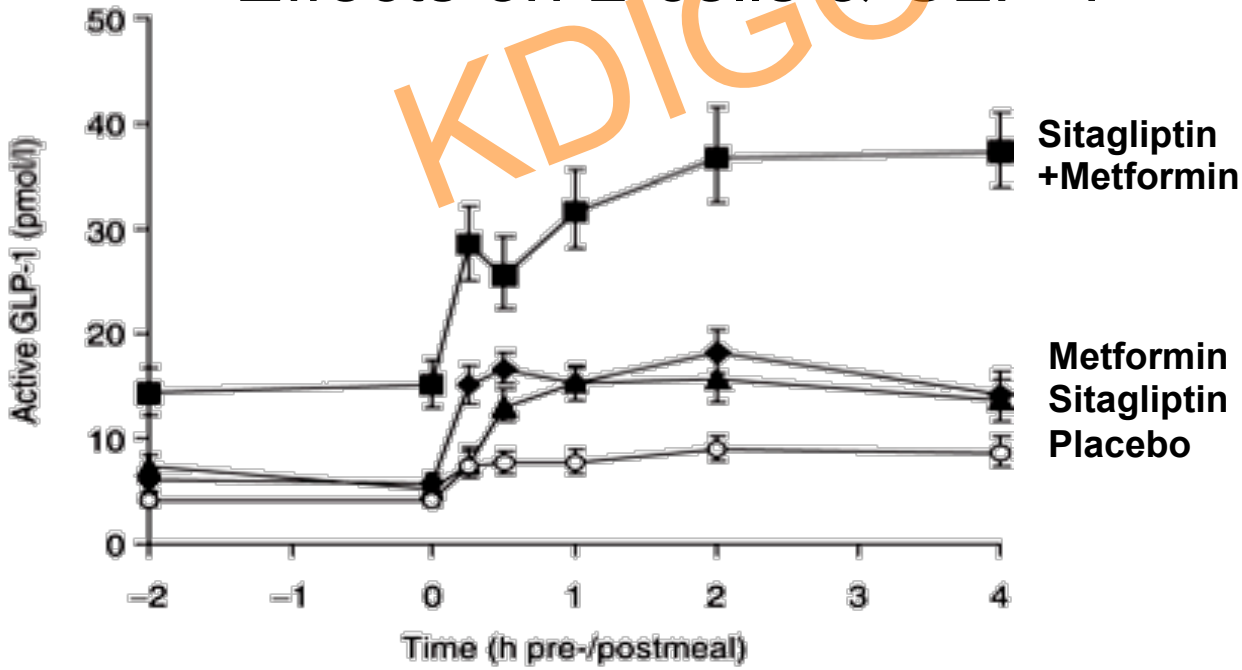
JAMA. 2014;312(24):2668-2675. doi:10.1001/jama.2014.15298

METFORMIN in CKD

Some glucose lowering may be mediated through the enteroendocrine axis.

Effects on microbiobe? Folate/methionine metabolism

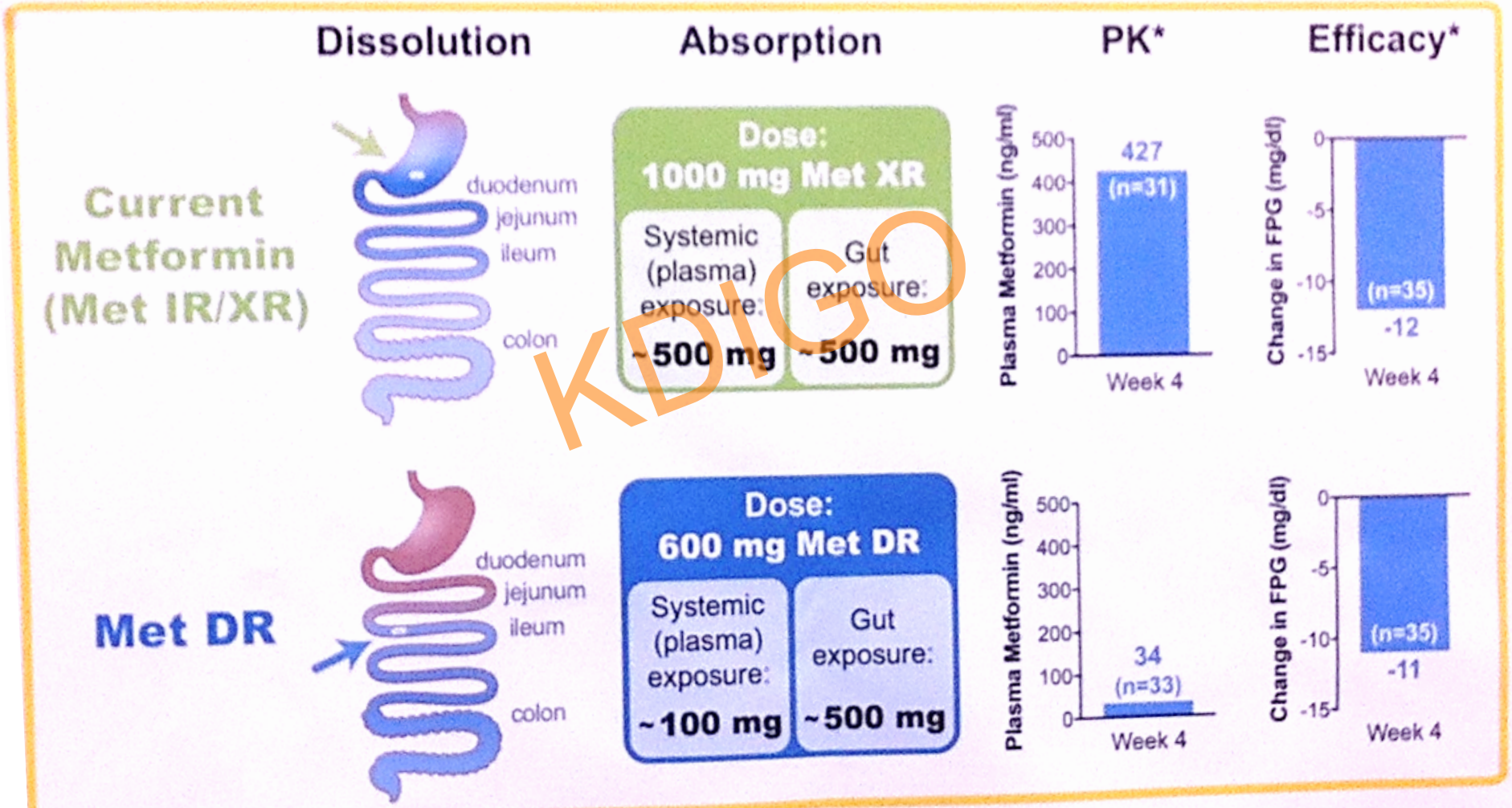
Effects on L-cells & GLP-1



1. Gao et al. Diabetes Obesity & Metabolism (2013). 2. Migoya et al. Clin Pharmacol Ther (2010)

elcelyx™

Figure 1. Glucose-Lowering Effect of Metformin is not Associated with Systemic (Plasma) Exposure: Phase 2 Randomized Placebo and Active Comparator Controlled Study LCRM105[1]



*Fasting plasma metformin (PK) data are median concentrations and efficacy data are the median change after 4 weeks of treatment.[1]
Abbreviations: Met IR = metformin immediate-release, Met XR = metformin extended-release, Met DR = metformin delayed-release, FPG = fasting plasma glucose.

- **These effects of Met DR support a gut-mediated mechanism of metformin action.[5]**

SULPHONYLUREA/INSULIN in CKD

- ☑ CHEAP
- ☑ TITATABLE EFFICACY

- ☒ ACCUMULATION/ADJUSTMENT
- ☒ INFLEXIBILITY
- ☒ ↑ HYPOGLYCAEMIA
- ☒ ↑ WEIGHT
- ☒ CARDIOVASCULAR EFFECTS?

Insulin clearance in CKD

- Most subcutaneous insulin is cleared by the liver
- But up to half may be cleared by the kidneys (60% filtered + 40% active tubular secretion)
- Insulin half-life is a "test of kidney function"
- The glucose-lowering effects of insulin and secretagogues carry over beyond post-prandial
- Despite greater insulin resistance
  - eGFR 30–45 ml/min/1.73 m^2: Need ~10% less insulin
  - eGFR 15–30 ml/min/1.73 m^2: Need ~25% less insulin
  - eGFR <15 ml/min/1.73 m^2: Need ~50% less insulin

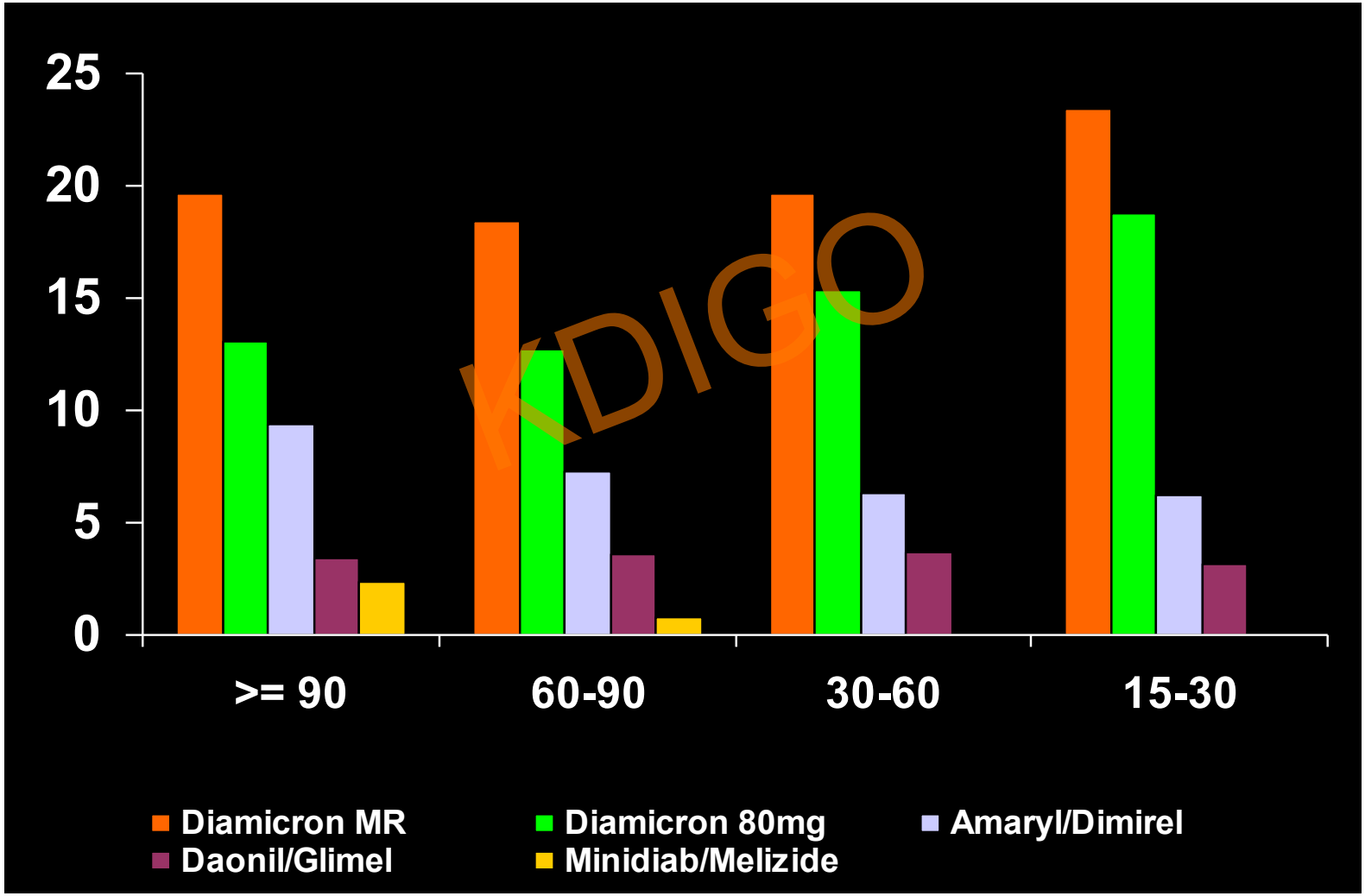
SULPHONULUREAS

Glibenclamide (= glyburide) (Daonil®; 2.5–10 mg/day) is metabolised by the liver, and is eliminated equally in bile and urine. Some of its metabolites are active and may accumulate in CKD although hepatobiliary elimination may partially compensate for the decrease in renal elimination. Glibenclamide is contraindicated in ≥3 CKD stages (eGFR <60 ml/min).

Glimepiride (Amaryl®, 1–8 mg/day) is metabolised by the liver to two main metabolites, one of which has hypoglycaemic activity. In patients with renal impairment, these metabolites can accumulate. The use of glimepiride is contraindicated in patients with a GFR of <60 ml/min.

Gliclazide (Diamicron® 80–320 mg/day; DiamicronMR® 30–120 mg/day) is metabolised by the liver to inactive metabolites, which are eliminated mainly in the urine (80%). Gliclazide poses a lower risk for severe hypoglycaemia than glibenclamide and glimepiride. But is still recommended to be stopped when GFR<40ml/min

Sulphonylurea use in general practice



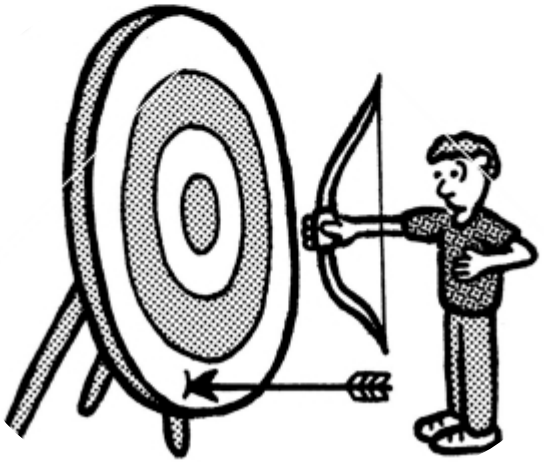
Risks for severe hypoglycemia (in the ADVANCE study)

- Increased age
- Prolonged duration of diabetes
- Renal impairment
- Albuminuria
- Lower BMI and cognitive function
- Use of multiple glucose-lowering drugs
- History of smoking

Zoungas S, et al. *N Engl J Med* 2010;363:1410–1418.

THE CHALLENGE OF CKD IN DIABETES

RIGHT RATIONALE
RIGHT TARGET/INTENSITY
RIGHT DRUG (S)
RIGHT DOSE
RIGHT MONITORING/PRECAUTIONS



TIME BETTER SPENT ELSEWHERE?