How to prescribe drugs in patients with Chronic Kidney Disease (CKD 2, 3, 4 and 5D)

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The 25th Budapest Nephrology School
26-31 August, 2019

1.

PLOS ONE July 6, 2016

RESEARCH ARTICLE

Global Prevalence of Chronic Kidney Disease – A Systematic Review and Meta-Analysis

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Chronic kidney disease (CKD) is a global health burden with a high economic cost to health systems and is an independent risk factor for cardiovascular disease (CVD). All stages of CKD are associated with increased risks of cardiovascular morbidity, premature mortality, and/or decreased quality of life. CKD is usually asymptomatic until later stages

« Increased CKD prevalence partly due to the ageing population
but
is also associated with increases in HTA and diabetes mellitus »

PLAN

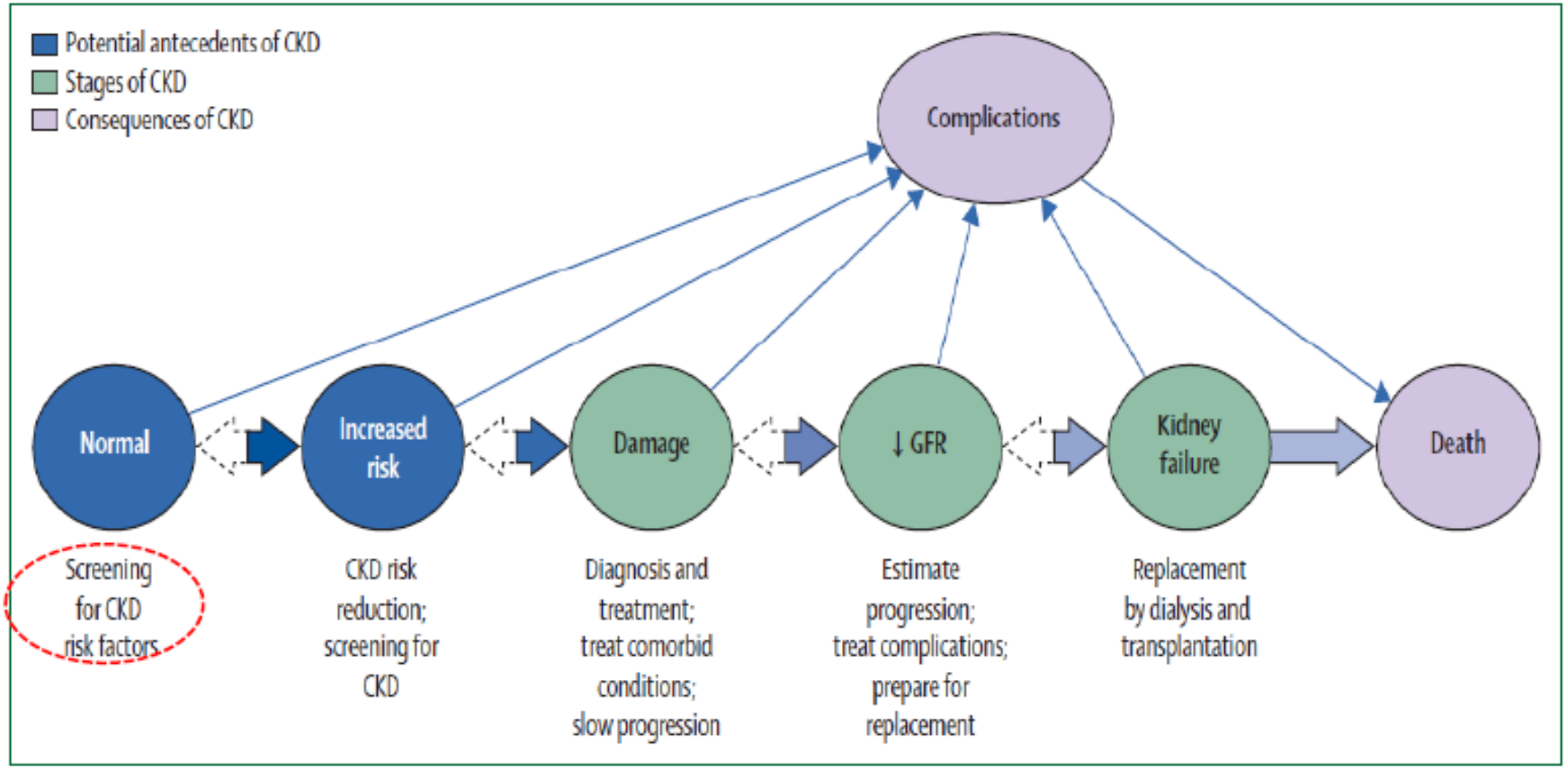
1. CKD stages
2. Assessment of Kidney Function
3. Pharmaco-kinetic & dynamic changes in CKD
4. Drug dosing adjustment in CKD
5. Factors associated with increased risk for nephrotoxicity
6. Take home messages

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 December 2015
EMA/CHMP/83874/2014
Committee for Medicinal Products for Human use (CHMP)

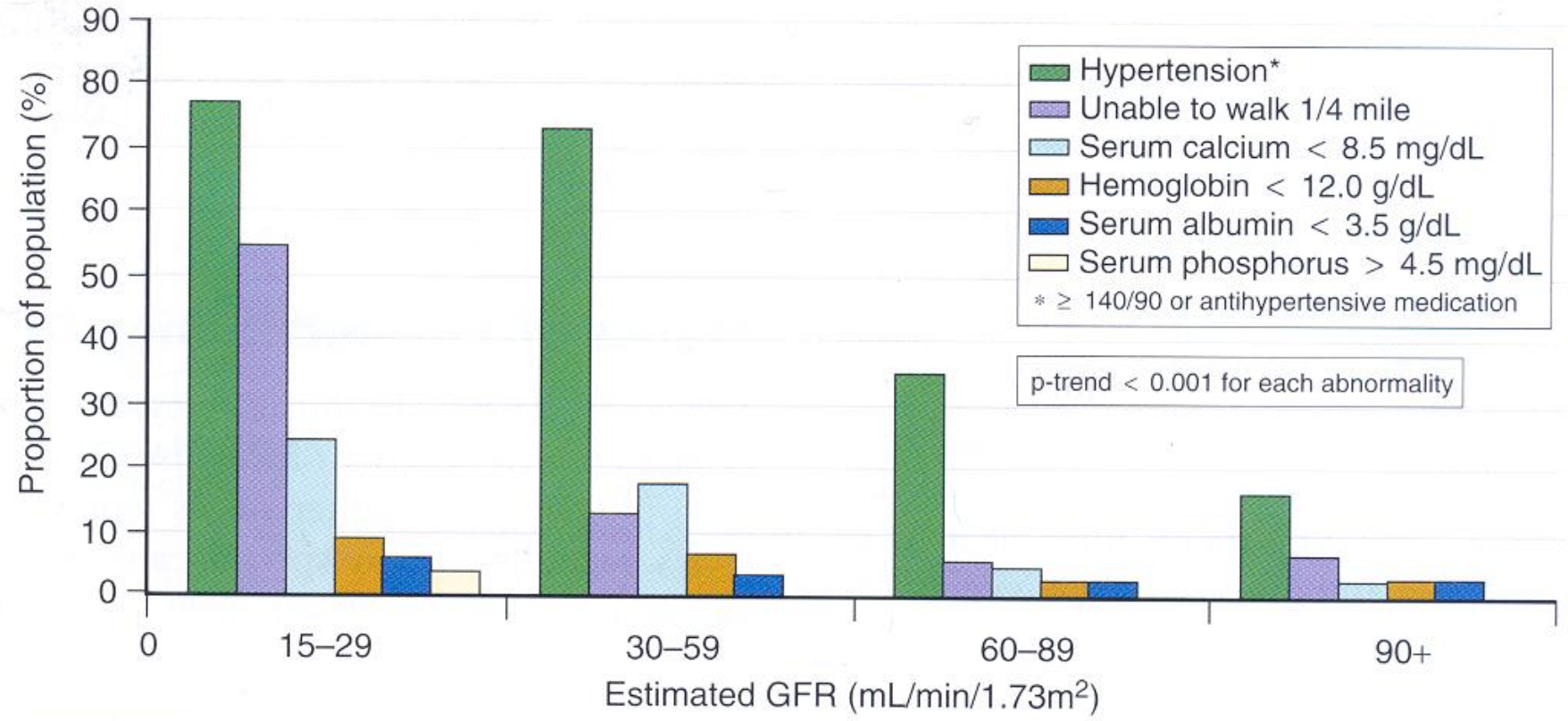
Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with decreased renal function

1. Model for stages in the initiation and progression of CKD and therapeutic interventions

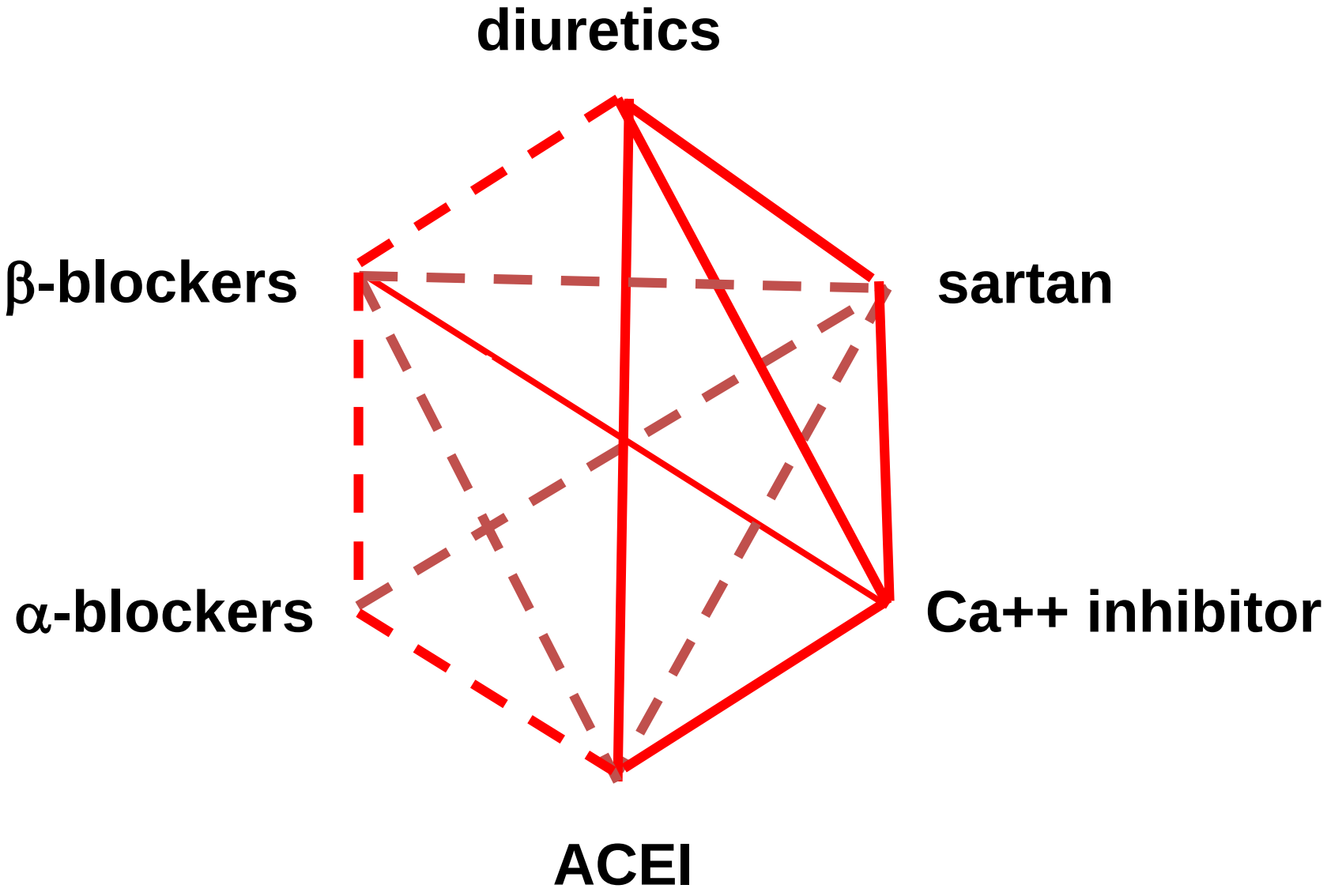


National Kidney Foundation

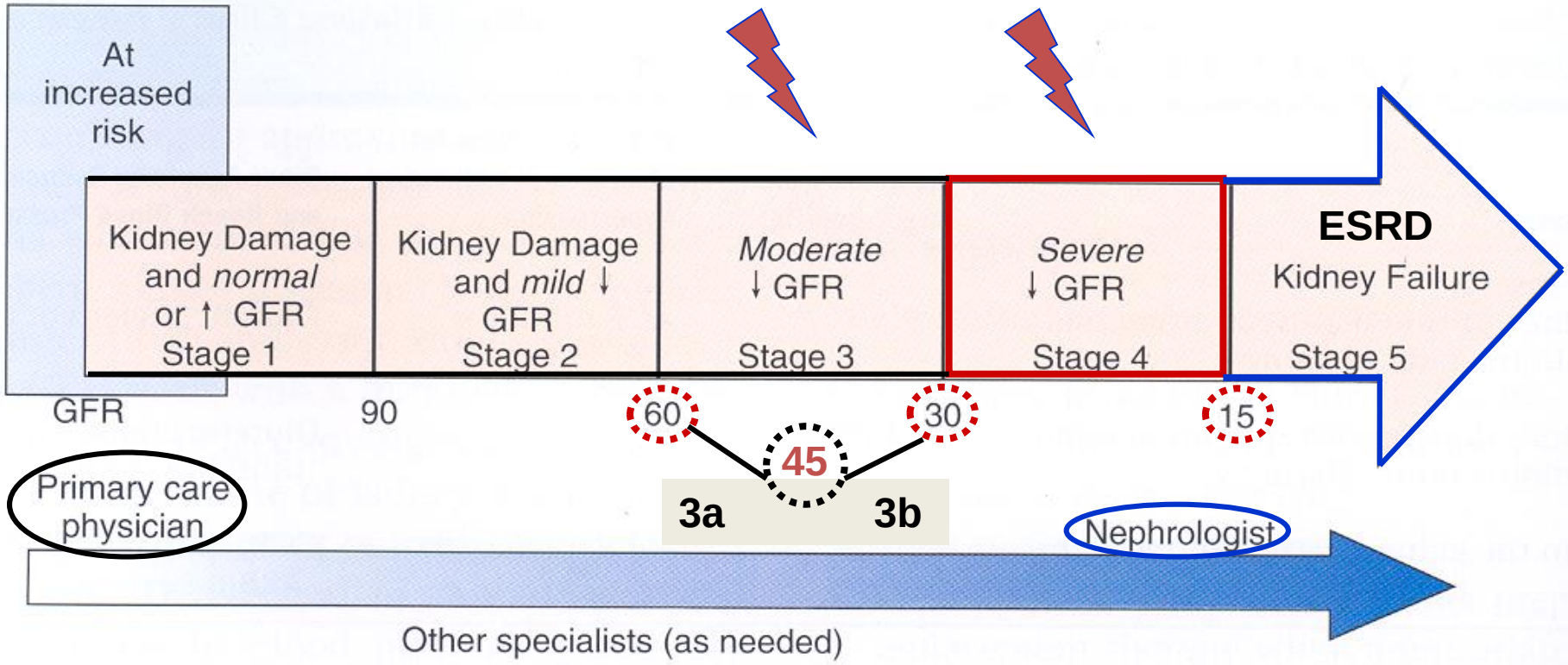
Importance of blood pressure control in CKD



THE BEST ANTIHYPERTENSIVE DRUG ASSOCIATIONS…



CKD staging based on eGFR equations



Estimated body surface area-normalised GFR: glomerular filtration rate (ml/min/1.73 m2)

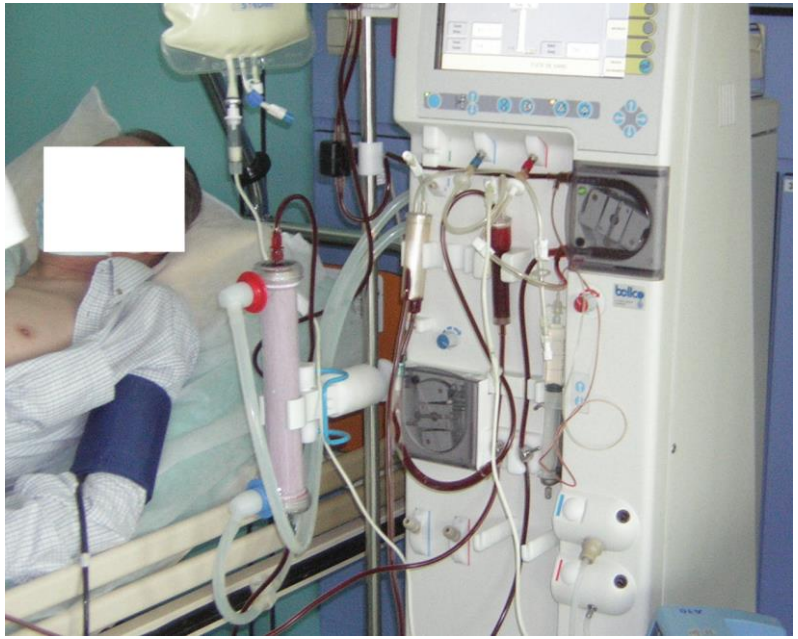
KDOQI (2002) and NICE (2008) recommendations

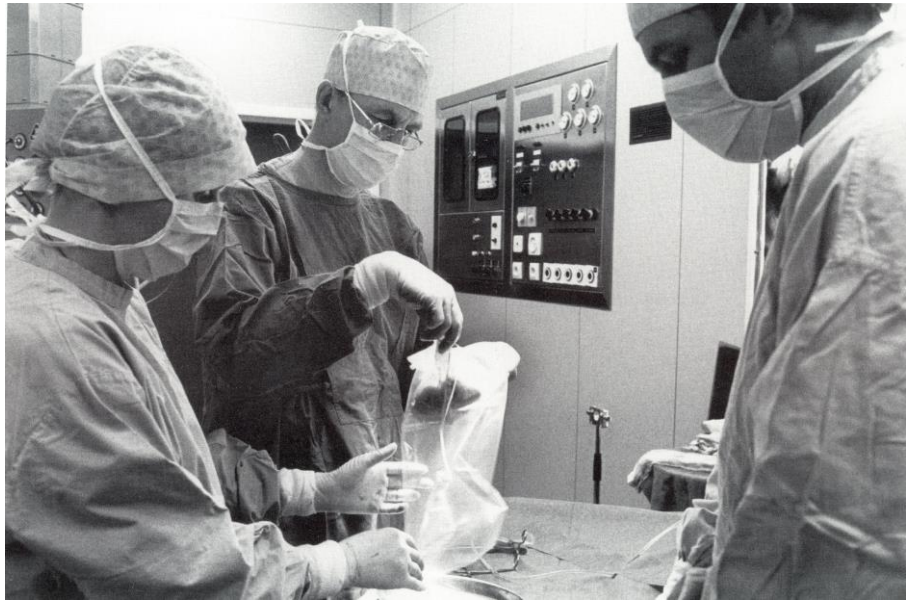
GFR categories (ml/min/1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90		Monitor	Refer*
	G2	Mildly decreased	60–89		Monitor	Refer*
	G3a	Mildly to moderately decreased	45–59	Monitor	Monitor	Refer
	G3b	Moderately to severely decreased	30–44	Monitor	Monitor	Refer
	G4	Severely decreased	15–29	Refer*	Refer*	Refer
	G5	Kidney failure	<15	Refer	Refer	Refer

Referral decision making by GFR and albuminuria. *Referring clinicians may wish to discuss with their nephrology service depending on local arrangements regarding monitoring or referring.

1. Kidney Disease : Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;1-150.

Stage 5D or 5T ⟺ *extrarenal depuration (dialysis)*





<u>or</u>

transplantation

2. Assessment of Kidney Function

Necessary to:

- Determine CKD stage
- Follow trends in progression of kidney disease
- Determine drug dosing adjustment

Assessment of Kidney Function

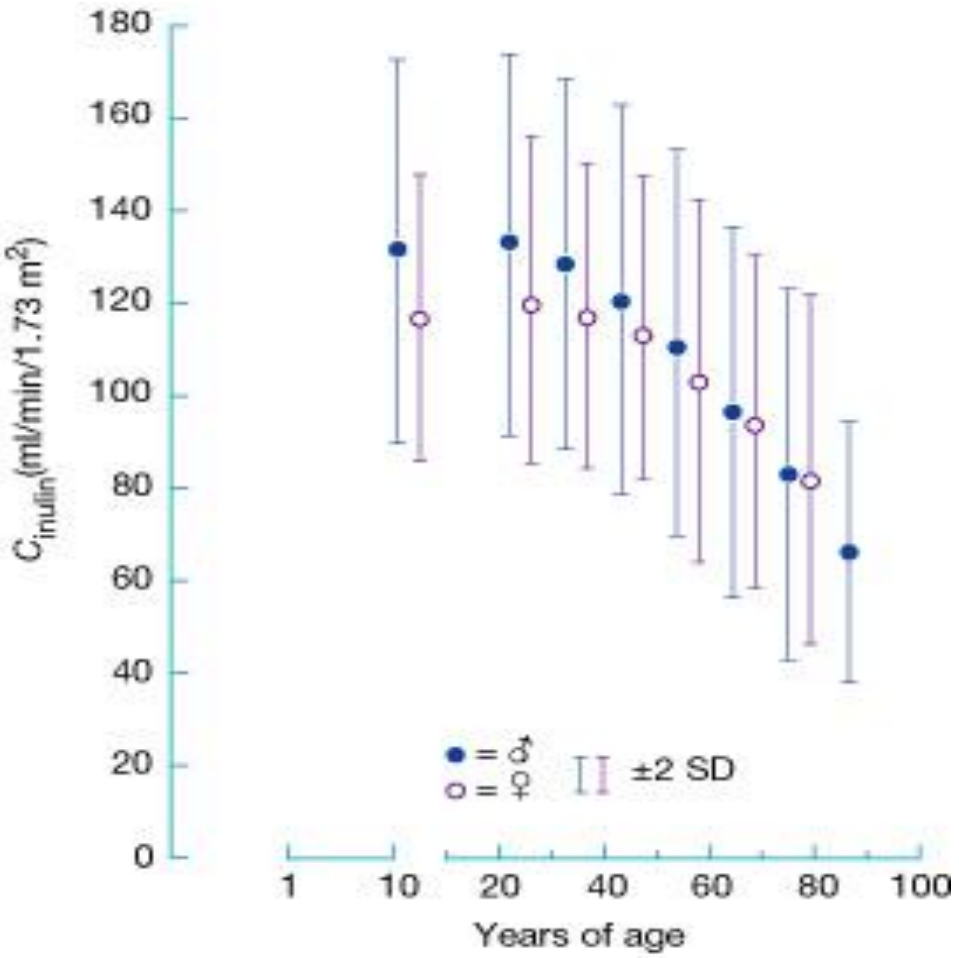
- Glomerular filtration rate (GFR) considered best clinical index of kidney function

Renal excretion = Glomerular filtration + Tubular secretion - Tubular reabsorption

A crucial choice !!!

- Inulin 'gold standard' for measured GFR (research)
- eGFR equations used (clinical practice)
- CKD staging system based on GFR
- GFR also used to assess kidney function for purpose of drug dosing

MEASURING GFR WITH INULIN

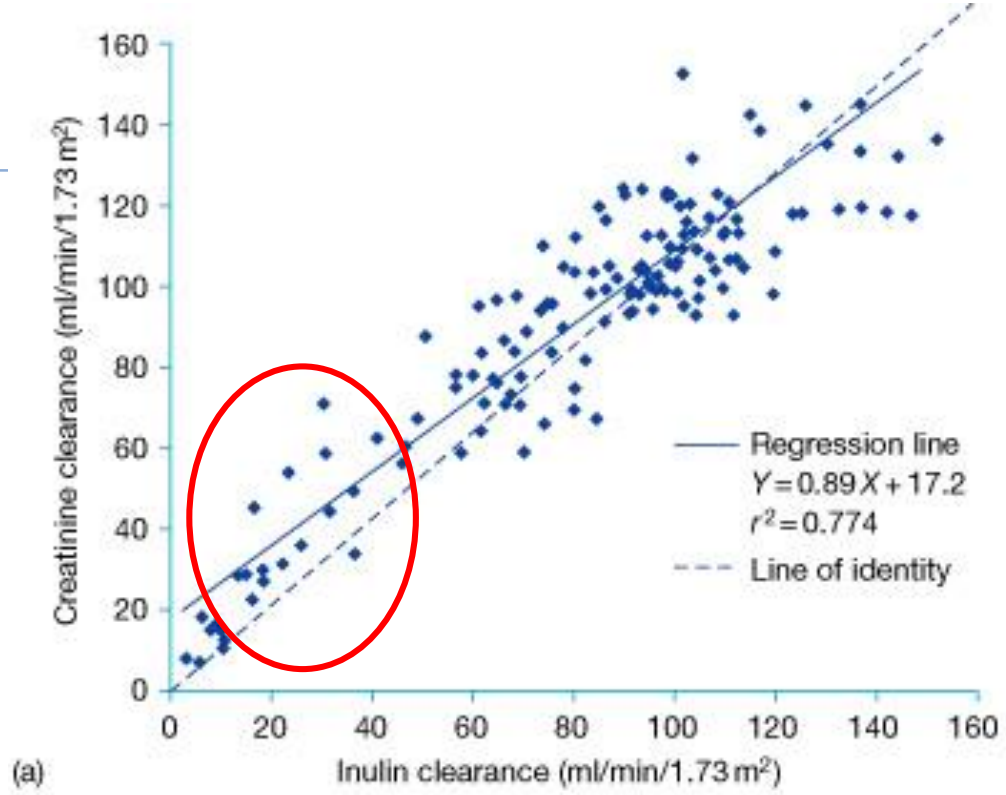


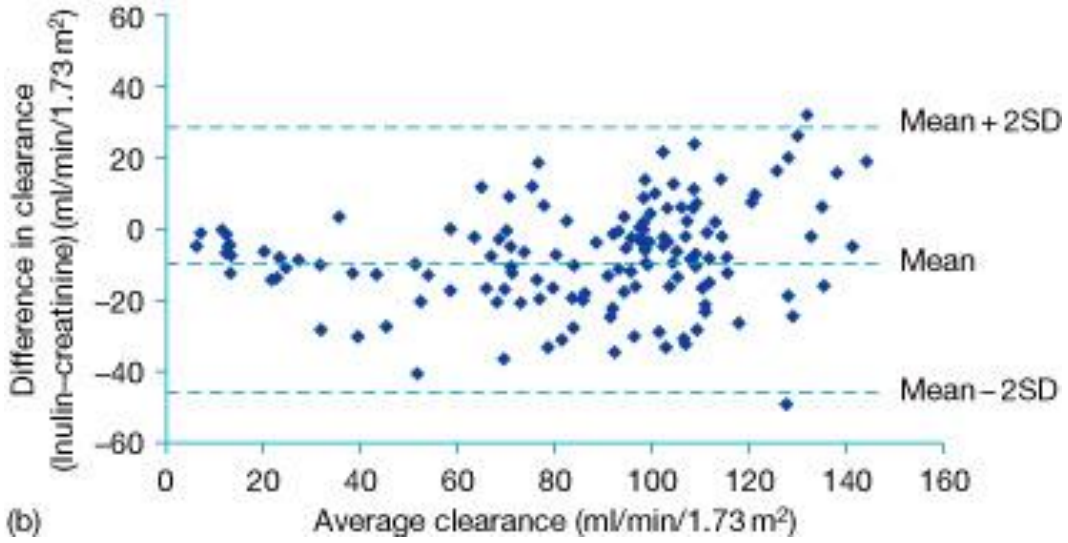
- Marker of glomerular filtration: **inulin** = exogenous substance nor reabsorbed nor secreted by the tubule
- **Inulin** clearance

  = (U x V) / P

  in ml/min/1.73 m2

NB: other exogenous substance used : **Iohexol, iodothalamate**





In practice …

Creatinine Clearance measured on 24h urine collection

$$Cl\ creat = (\dot{U} \times V) / P \quad (ml/min)$$

U= urinary creatinine (mg/dl)

$\dot{V}$= urinary excretion rate (ml/min)

P= plasma creatinine (mg/dl)

Due to increased tubular secretion of creatinine, creatinine clearance overestimates GFR at advanced stages of CKD !

ESTIMATING GFR FROM ENDOGENOUS MARKERS

!! Determination of plasma (or serum) creatinine

Pcreat: 0.8 – 1.1 mg/dl [UI: 70 à 106 µmol/l]

Cockroft & Gault formula

→ Calculated creatinine Clearance

$$Cl\ creat = \frac{140 - age\ (years) \times body\ weight\ (kg)}{72 \times Pcreat\ (mg/dl)}\ \text{in ml/min}$$

[women: x 0.85]

Abbreviated MDRD *(aMDRD)* → *estimated GFR*

$$eGFR = k \times 186 \times [Screat]^{-1.154} \times [age]^{-0.203}$$

k=1 (male) or 0.742 (female)

- Drug-dose modification in CKD utilizes measures of GFR with implicit assumption that all renal excretory processes (GFR, TS and TR) decline in parallel as CKD progresses
- Elimination of many drugs (e.g. cephalosporins & penicillins, loop diuretics) are dependent on TS for some or all clearance

Does GFR decline in parallel with TS?

- Systematic analysis
- Of 21 drugs where ratio of total CLr to $CL_{filtration}$ (Rnf) >0.74 with normal kidney function
  - Implies drug is both filtered and secreted)…
  - 13 displayed significant change in Rnf vs. GFR
- Conclusion: Failure of GFR to predict changes in TS in over 50% of drugs evaluated
- Implication: under or overdosing may occur

Chapron A. Clin Transl Sci 2017;10,395-403.

TS: tubular secretion; TR: tubular reabsorption

Serum Creatinine (sCr) is an imperfect marker of GF

- Function of production (muscle), excretion (glomerular filtration and tubular secretion) and ingestion

Increased sCr	Decreased sCr
CKD	Reduced muscle mass (elderly, females)
African American vs others	Malnutrition
Drugs that inhibit tubular secretion: cimetidine, trimethoprim fenofibrate, probenecid	Amputation
Ingestion of meat protein or creatine supplements	Vegetarian diet

Stevens LA, et al. N Engl J Med 2006;354:2473-83.

Variables included in estimating eqns (age, sex, weight, race) improve prediction, but don't account for everything that cause variability from true GFR.

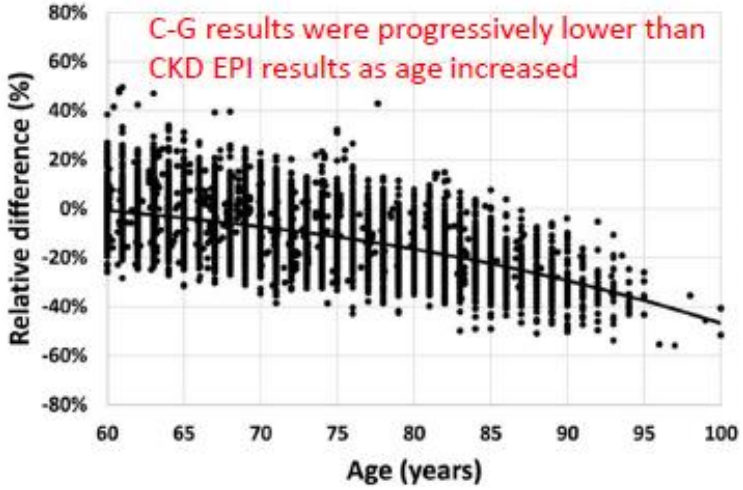
eGFR equations for adult general population used for drug dosing

Equation	Variables	Normalized to BSA 1.73m^2?	Comments
Cockcroft-Gault CrCL (1976)	sCr, age, sex, weight*	No	Can't be re-expressed for standardized sCr
Re-expressed MDRD (2007)	sCr, age, sex, black or non-black	Yes	Provides better estimate of mGFR than mCrCl or eCrCl
CKD-EPI$_{creatinine}$ (2009)	sCr, age, sex, black or non-black	Yes	Less biased than MDRD with GFR >60
Measured CrCL	sCr, uCr, urine volume, collection time	No	Less accurate than eGFR equations in general pop, but may be more accurate in specific patients**

*weight parameter used varies widely (e.g. total body wt, ideal body wt, adjusted body wt)
**amputees, malnourished, body builders, vegetarians, low muscle mass, on drugs that undergo TS

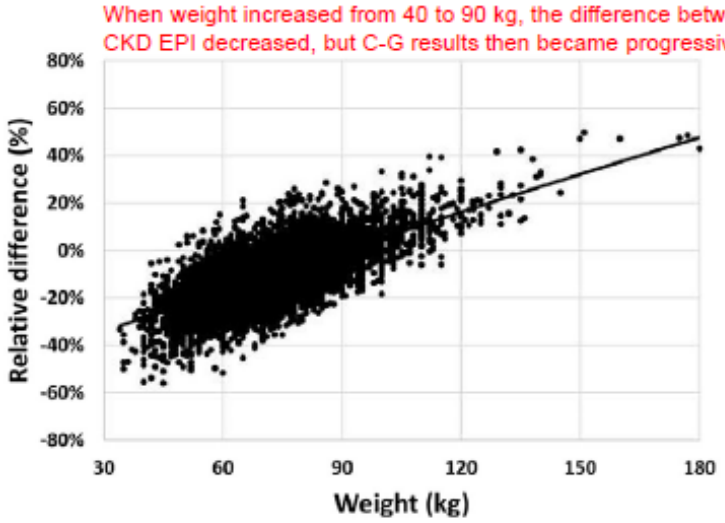
Equation	Formula	Estimate of:
Cockcroft-Gault (CG) (1976)	(140-age) x Wt (kg) x 0.85 if female SCr x 72	eCrCL (mL/min)
Re-expressed MDRD (2007)	175 x SCr$^{-1.154}$ x age$^{-0.203}$ x (0.742 if female) x (1.21 if African-American)	eGFR (mL/min/1.73 m^2)
CKD-EPI$_{Creatinine}$ (2009)	141 x min(SCr/κ,1)$^{\alpha}$ x max(SCr/κ,1)$^{-1.209}$ x 0.993^{Age} x 1.018 [if female] x [1.159 if black]	eGFR (mL/min/1.73 m^2)
CKD-EPI$_{Cystatin\ C}$ (2012)	eGFR$_{Cys}$ (mL/min/1.73 m^2) = 133 x min(Scys/0.8,1)$^{-0.499}$ x max(SCys/0.8,1)$^{-1.328}$ x 0.996^{Age} x 0.932 [if female]	eGFR (mL/min/1.73 m^2)
CKD-EPI$_{Creatinine\text{-}Cys\ C}$ (2012)	eGFR$_{Creat\text{-}Cyst}$ (mL/min/1.73 m^2) = 135 x min(Scr/κ,1)$^{\alpha}$ x max(Scr/κ,1)$^{-0.601}$ x min(Scys/0.8,1)$^{-0.375}$ x max(SCys/0.8,1)$^{-0.711}$ 0.995^{Age} x 0.969 [if female] x 1.108 [if black]	eGFR (mL/min/1.73 m^2)

Effect of age on relative differences b/t C-G and CKD EPI



Delanaye P. Clin Pharmacokinet 2017;56:193.

Effect of weight on relative differences b/t C-G and CKD EPI



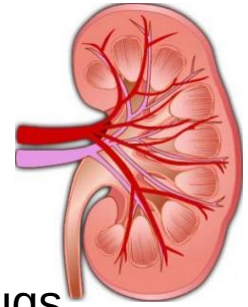
Delanaye P et al. *Clin Pharmacokinet* 2016;Jul 14. [Epub ahead of print]

C-G: Cockroft and Gault

In summary

- Individualize drug dosing using most appropriate kidney function assessment
  - Narrow therapeutic index: consider mCrCL or mGFR
- Weight and age are main predictors of discrepancies between C-G and CKD-EPI
- In Elderly
  - Use of CKD EPI or MDRD overestimates doses
    - Overestimation increases as age increases
  - Adjusting CKD EPI or MDRD for patient's BSA will generally improve dose concordance with C-G
- In Obesity
  - TIA weight choice reduces bias & improves accuracy of C-G results
  - CKD EPI and MDRD with BSA adj is similar to $C\text{-}G_{ABW0.4}$

3. Modifications of pharmacokinetic parameters in CKD



1. ABSORPTION

↓ HCl is frequent in severe CKD ⇒ gastric reabsorption of several drugs may be reduced

2. DISTRIBUTION : Volume of distribution variations !

↑ Free fraction of drug in plasma in case of hypoalbuminemia (e.g. nephrotic syndrome): increased risk of toxicity of drugs bound ++ to plasma proteins such as sulfamides and coumarin agents

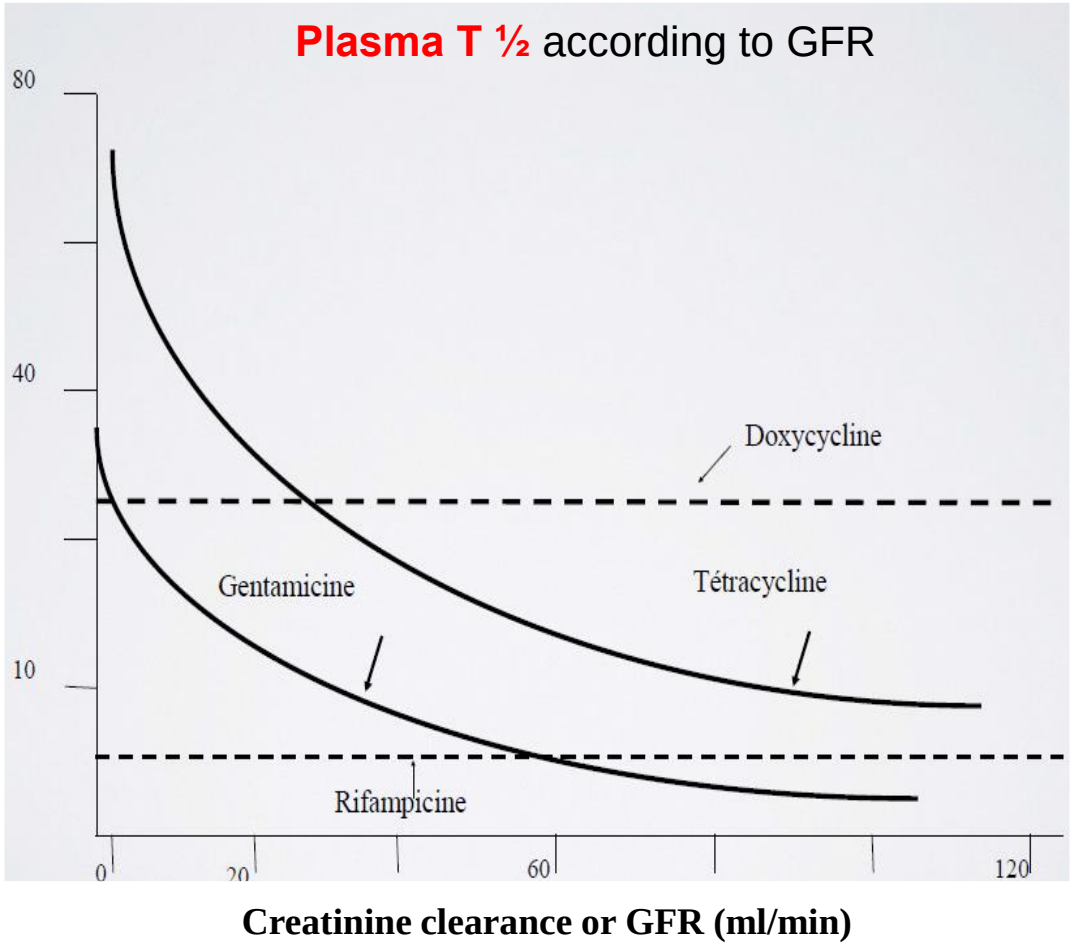
↑ Extracellular compartment due to edema (salt retention)

3. METABOLISM

↓ first liver passage (? effect of uremic toxins on hepatic enzymes)

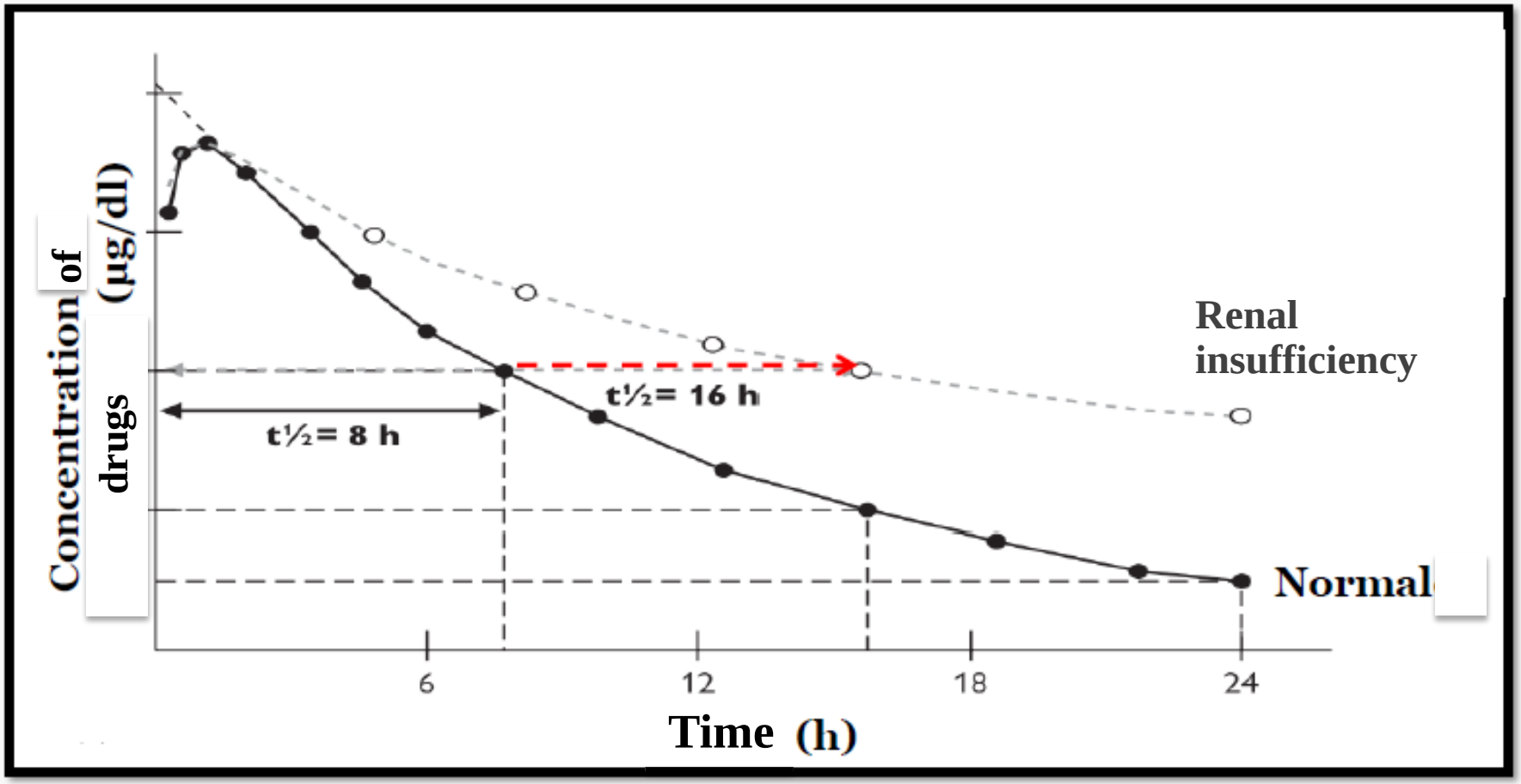
4. Elimination: concerns drugs (active form or active metabolite) with renal elimination

Elimination ↓ ⇒ ↑ T ½ of drugs with accumulation risk ⇒ ↑ effect and ↑ risk of toxicity



- Tetracycline and gentamicine: almost exclusively eliminated in their active form by the kidney
- Rifampicine : entirely metabolised by the liver
- Doxycycline: eliminated unchanged (biliary route + kidney)

Renal Elimination ↓ ⇒ ↑ T ½ of drugs with risk of accumulation
⇒ ↑ effect and ↑ risk of toxicity = <u>pharmacodynamic consequences</u>



D'après Barratt J, Topham P, Harris KPG. Oxford desk reference : Nephrology. Oxford University Press

In case of moderate to severe CKD (3a and more) ⇒ drug dosing adjustment is necessary !

Digoxin, hydrophilic β-blockers (such as atenolol, nadolol, sotalol),
ACE inhibitors (mainly from stage 3b), spironoloactone, acetalozamide

Several antiepileptics (primidone, vigabatrine), paroxétine, lithium

Antihistaminics (mainly anti-H_2)

Insuline and analogues + biguanides (**see example of metformin)**

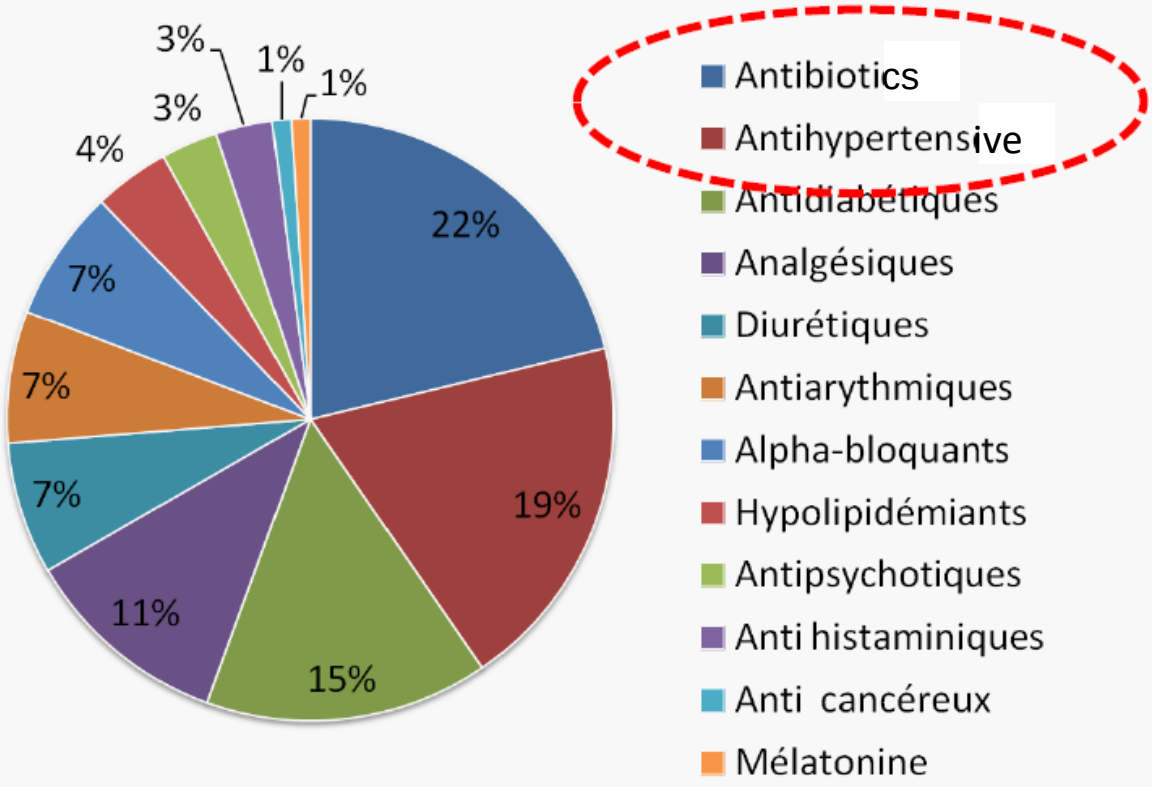
Several antiviral drugs such as aciclovir, ganciclovir

Antibiotics such as cephalosporins, amoxicillin, amoxicillin + clavulanic acid,
quinolones, triméthoprim, nitrofurantoïn

Fibrates, allopurinol, diphosphonates

Potentially inappropriate medications in elderly patients with CKD (PIMs)

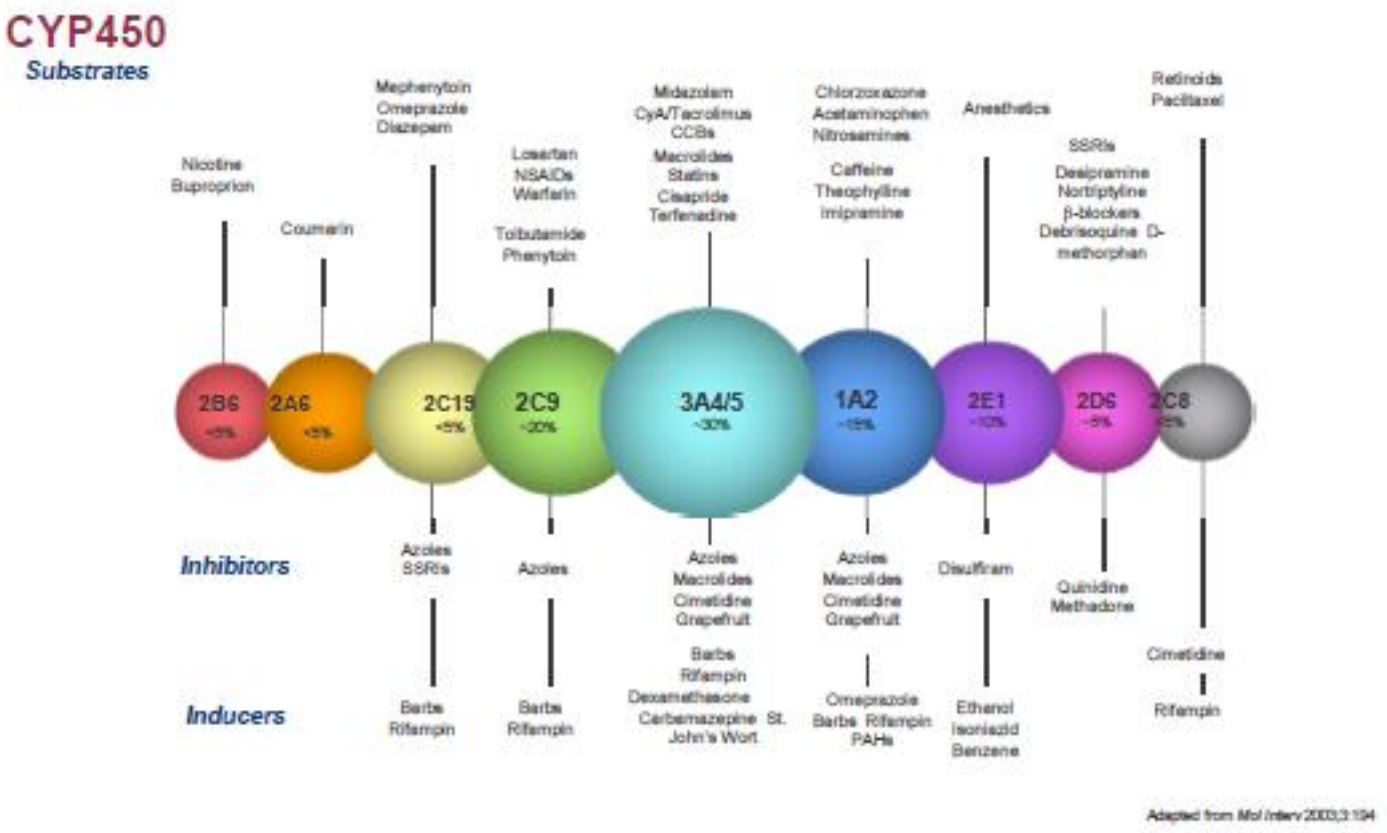
Percentage of distribution of PIMs within prescriptions of drugs



Jones SA, Bhandari S. The prevalence of potentially inappropriate medication prescribing in elderly patients with chronic kidney disease. Postgr Med J. 2013;89:247–50.

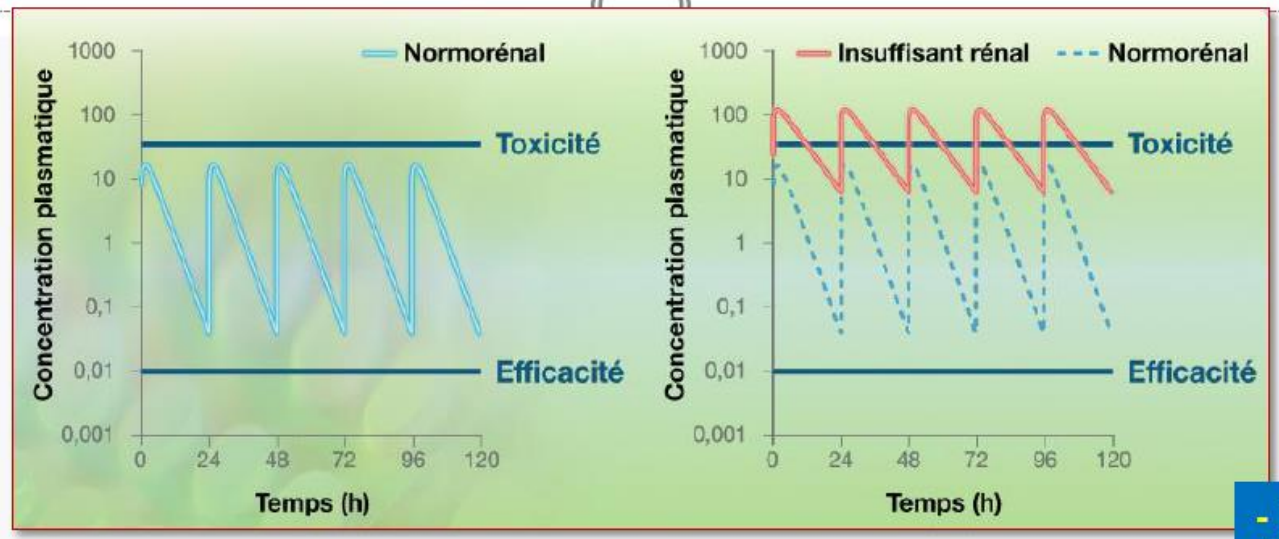
Why Nonrenal Clearance?

- Large contributor to total systemic clearance
- Comprised of metabolism and transport
- Metabolism mediated primarily by CYP450 (to lesser extent Phase II enzymes)
- Transport mediated by P-gp, OATP, MRP, OCT, OAT, etc



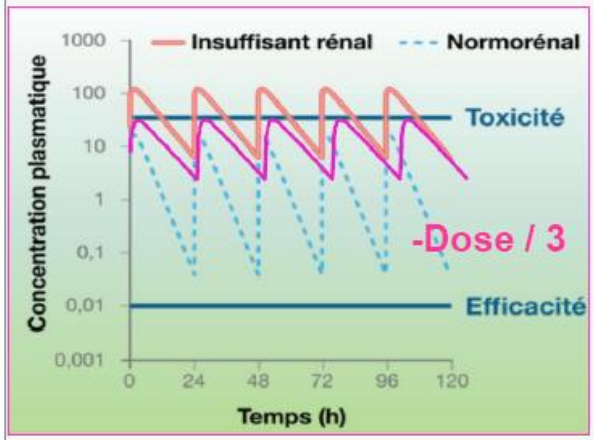
Adapted from *Mol Interv* 2003;3:194

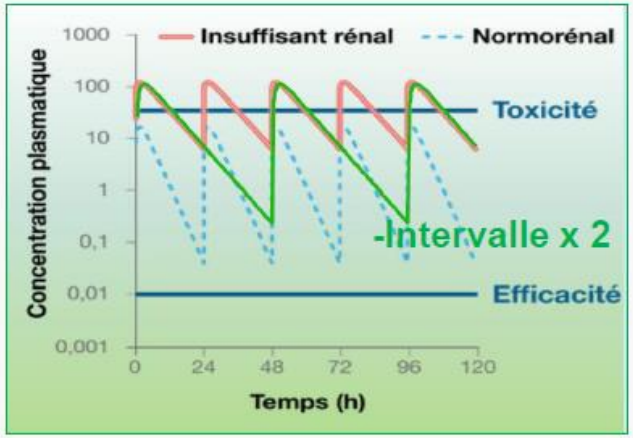
3. Drug dosing adjustment in CKD patients: efficacy and safety are the goals to achieve

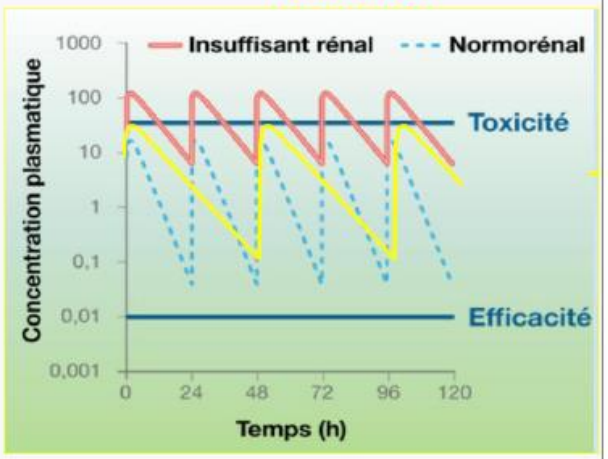


Therapeutic range

- Intervalle x 2 + dose / 3







Aloy B. Maniement des antibiotiques chez le patient insuffisant rénal: Actualisation des adaptations posologiques à la pratique clinique en infectiologie. La Lett d'ICAR. 2017;mai. Available from http://www.infectiologie.com/UserFiles/File/jra/jra-2017/jra2017-at04-atb-ir-alfandari-meyssonnier.pdf

1st option: ↑ time interval of administration : WHEN ?

- The therapeutic index is « comfortable » (large)

- The drug activity is related to a peak of concentration (this C_{max} could not be obtained by reducing the loading dose, e.g. aminosides)

- A through level can be measured and is necessary to avoid toxicity (increased $T_{1/2}$ of gentamicine): the prolonged time interval will result in eliminating the drug and its active metabolites

Time interval between 2 doses = Nl Creat Clearance x Nl time interval / patient's Creat Clearance

!! A prolonged time interval between 2 doses could favor periods with infra-therapeutic concentration

2nd option: ↓ individual dose: WHEN ?

- The therapeutic index is narrow (e.g. **digoxine**, **lithium**, **aminoglycosides**)
- $T_{1/2}$ is short and not increased in CKD (rapid elimination). If the time interval is increased, infra-therapeutic concentrations could be obtained (penicillines)
- A minimal or constant plasma level is required; the time interval must be unchanged in order to maintain this concentration

3rd option: ↑ time interval and ↓ doses

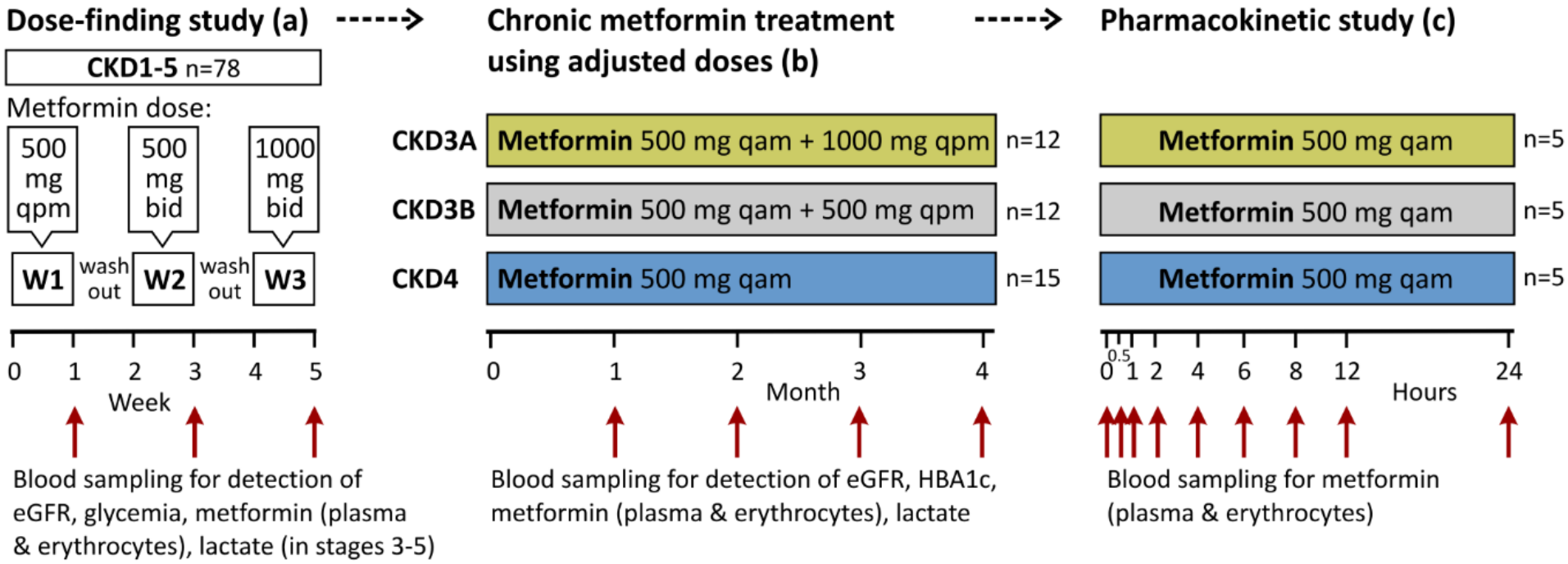
Ex. cephalosporins, metronidazole

Importance of designing and conducting full-range or staged PK studies in subjects with decreased renal function with a drug and/or active metabolite(s) expected to exhibit an increased exposure with clinically relevant effects !

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 30 ml/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

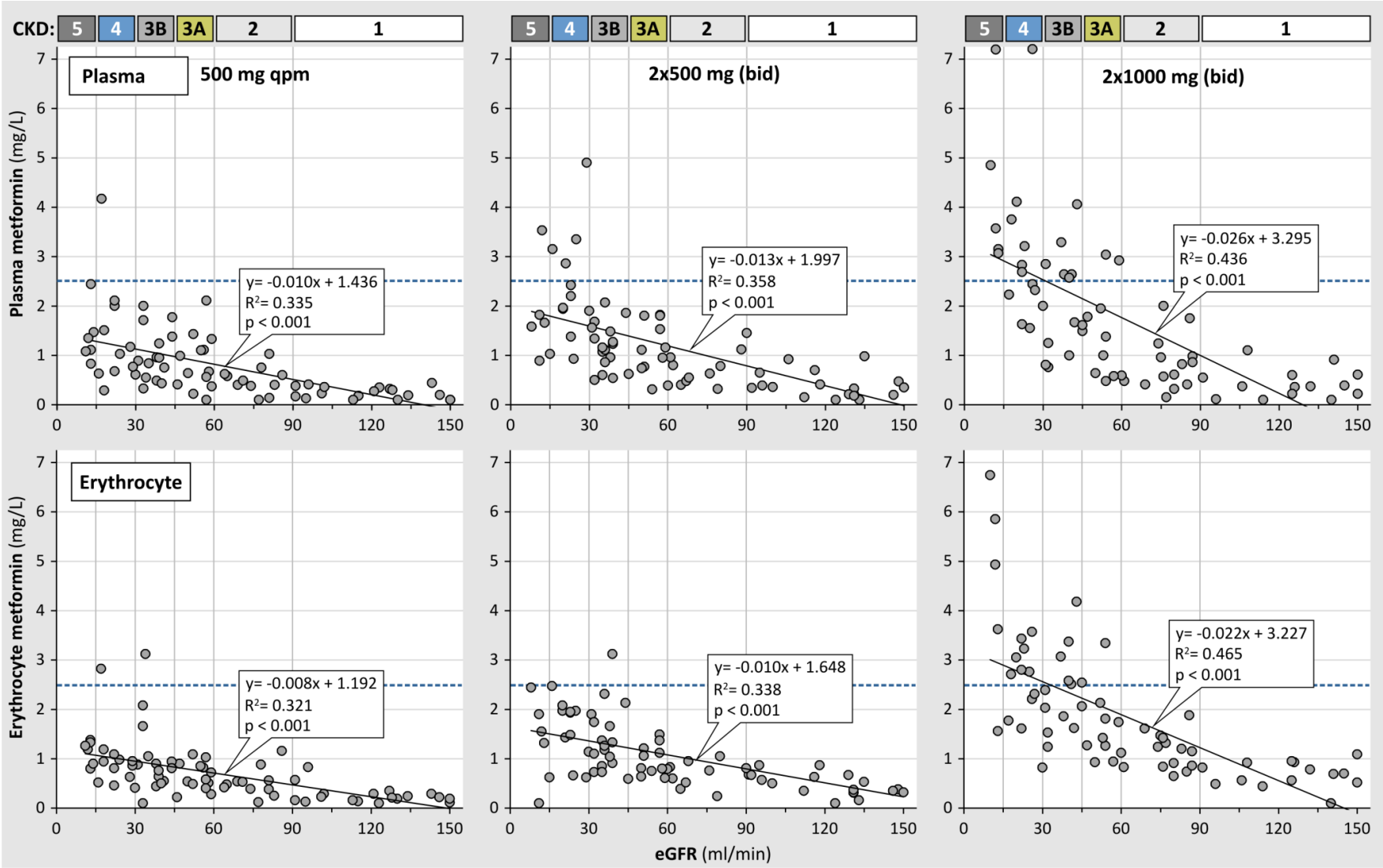
THERAPEUTIC CONCENTRATIONS OF **METFORMIN** A SYSTEMATIC REVIEW

- FDA 5 mg/l….”safety level “ metformin
- Mean plasma concentrations of metformin over a dosage interval be maintained below 2.5 mg/L (Cav, ss)
- Plasma lactate begins to increase when plasma metformin concentrations are greater than about 20mg/L
- Lactate levels < 5 mMol

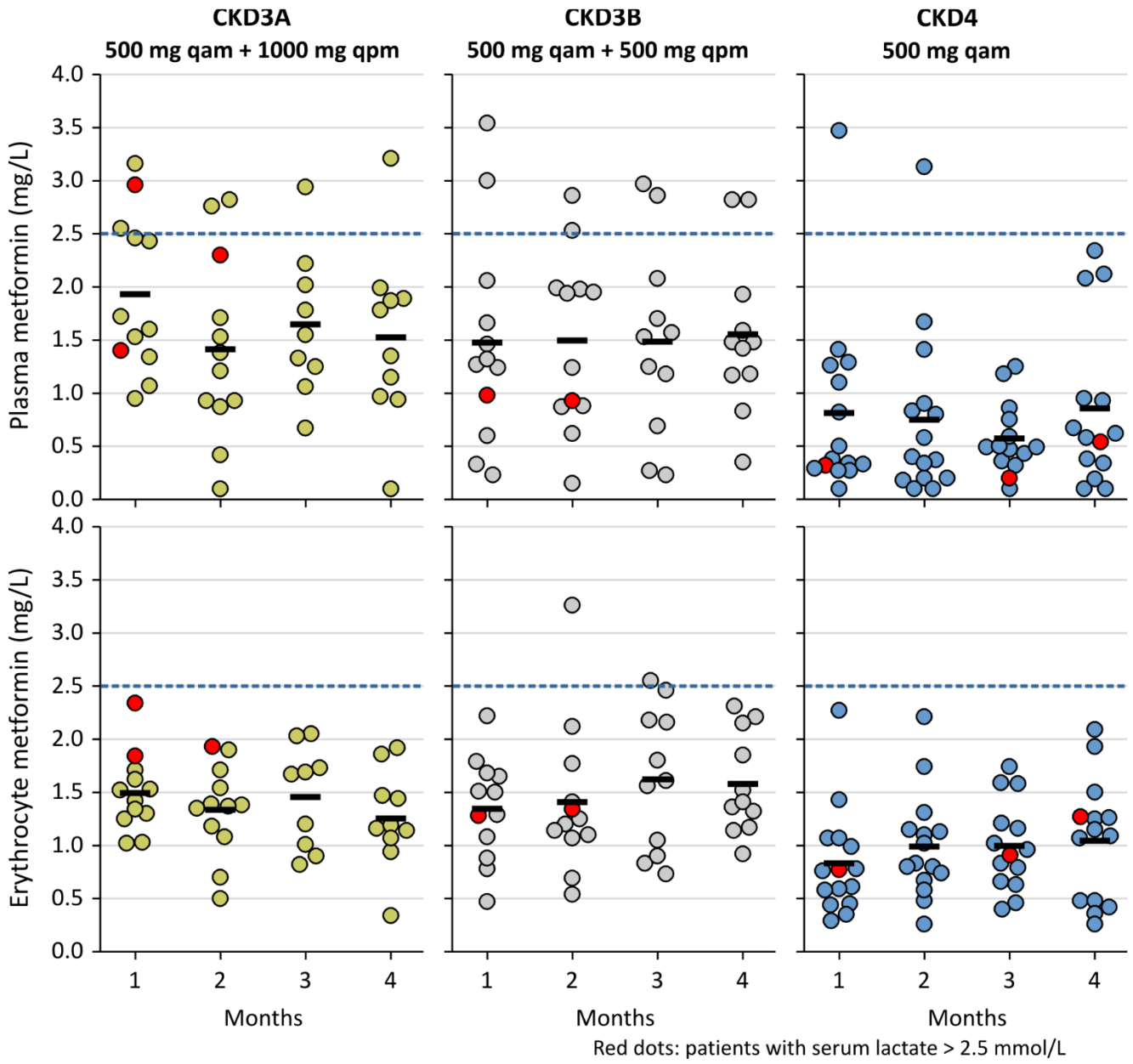
Kajbaf F, De Broe, M Lalau JD. Clin Pharmacokinet 2015
«CPKA-D-15-00143(1)» 2015

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



12 hr after the last dose

Below 5 mg /L

?

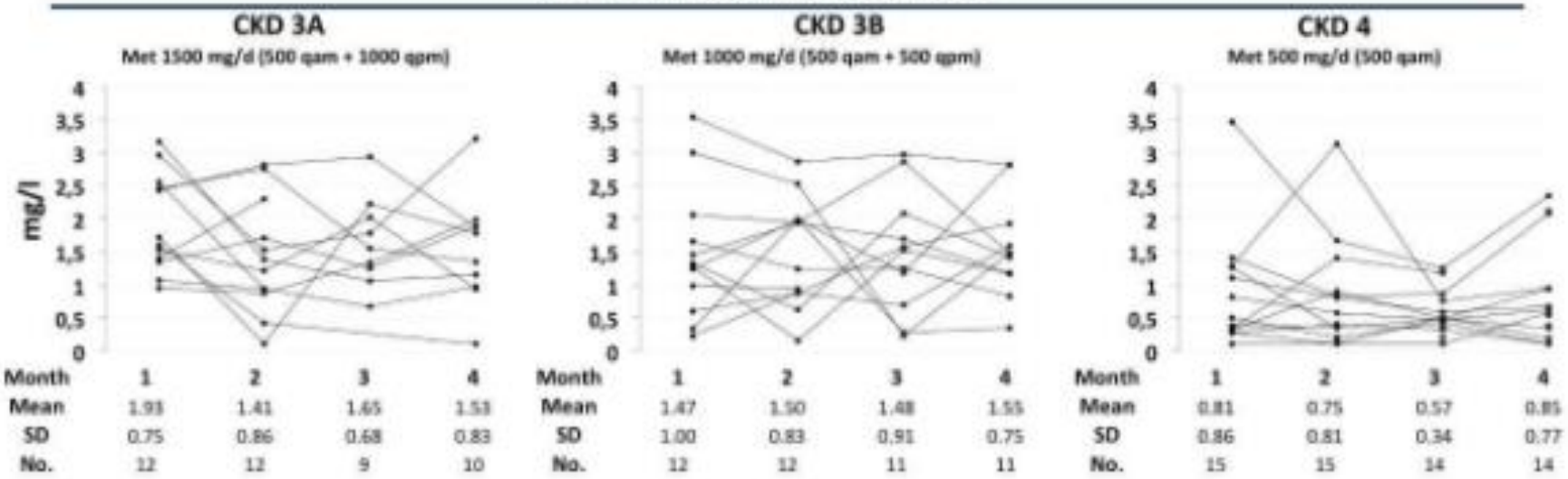
Lactic Acidosis > 5 mMol
pH < 7.35

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

A 4-MONTH METFORMIN THERAPY IN CKD WITH ADJUSTED DOSE

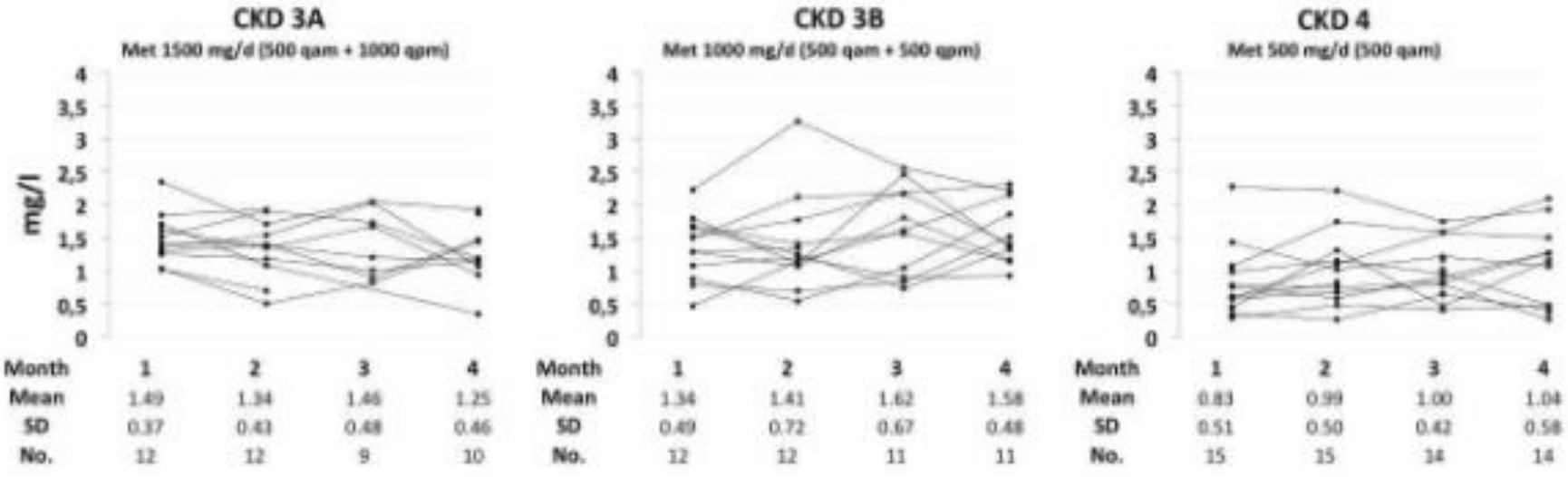
OCT transporters

1- Plasma metformin concentrations

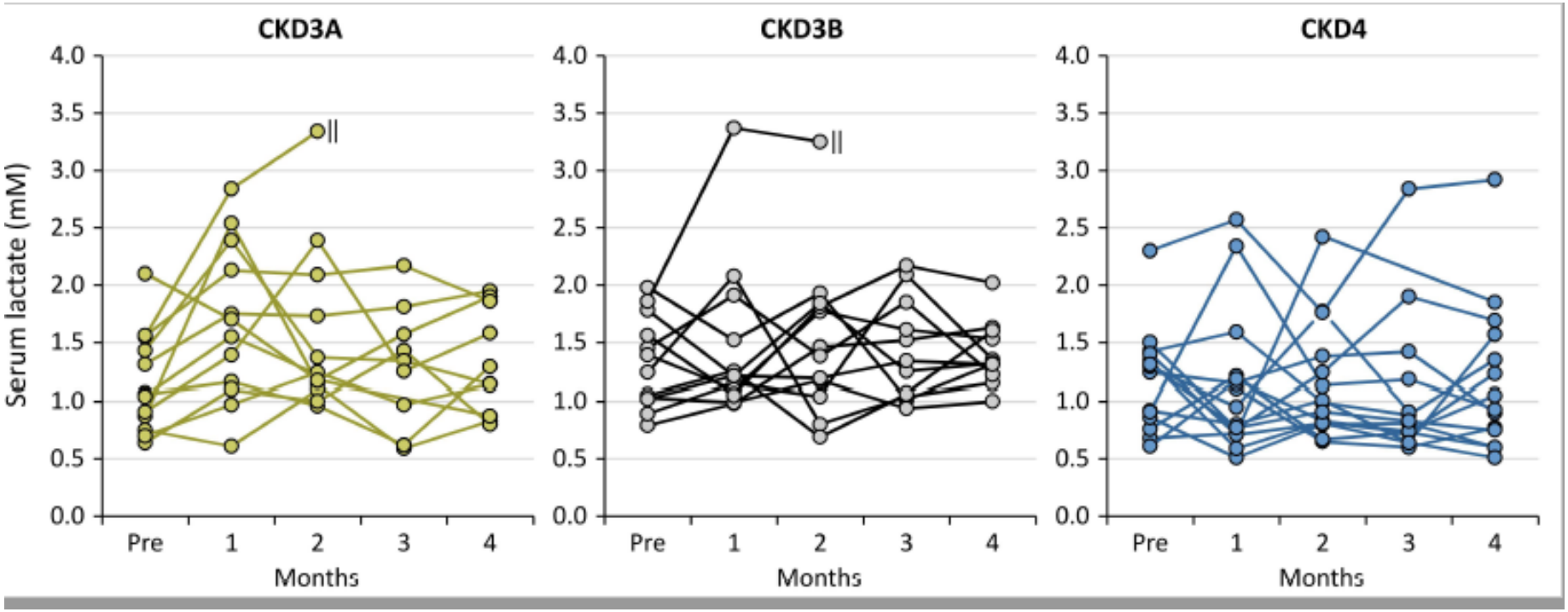


	CKD 3A				CKD 3B				CKD 4			
Month	1	2	3	4	1	2	3	4	1	2	3	4
Mean	1.93	1.41	1.65	1.53	1.47	1.50	1.48	1.55	0.81	0.75	0.57	0.85
SD	0.75	0.86	0.68	0.83	1.00	0.83	0.91	0.75	0.86	0.81	0.34	0.77
No.	12	12	9	10	12	12	11	11	15	15	14	14

2- Erythrocyte metformin levels

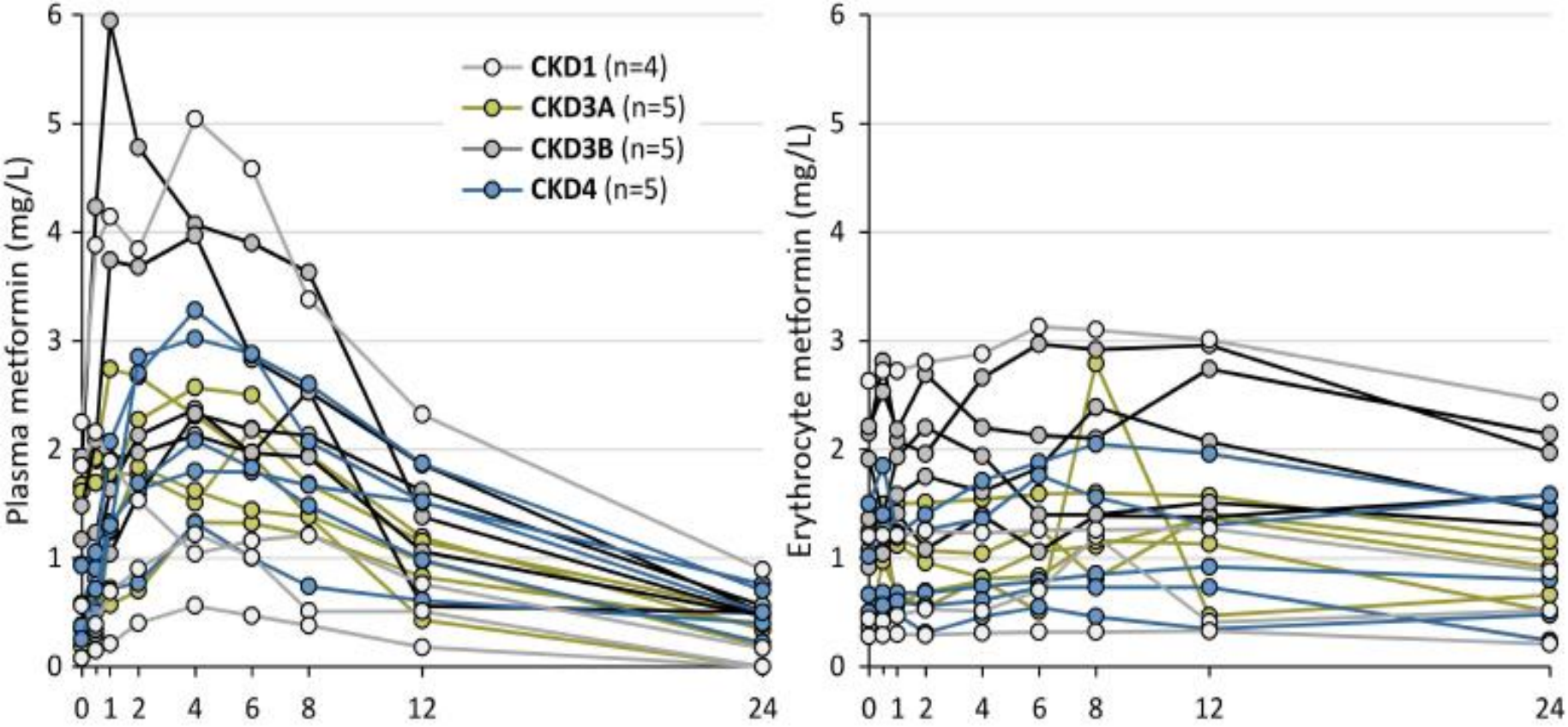


	CKD 3A				CKD 3B				CKD 4			
Month	1	2	3	4	1	2	3	4	1	2	3	4
Mean	1.49	1.34	1.46	1.25	1.34	1.41	1.62	1.58	0.83	0.99	1.00	1.04
SD	0.37	0.43	0.48	0.46	0.49	0.72	0.67	0.48	0.51	0.50	0.42	0.58
No.	12	12	9	10	12	12	11	11	15	15	14	14



Lactic Acidosis > 5 mMol ; pH < 7.35

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


Plasma metformin (mg/L)
Erythrocyte metformin (mg/L)
CKD1 (n=4)
CKD3A (n=5)
CKD3B (n=5)
CKD4 (n=5)
0
1
2
3
4
5
6
0 1 2 4 6 8 12 24

PARAMETERS OF THE PHARMACOKINETIC STUDY

1500 mg 1000 mg 500 mg

Parameters		CKD3A	CKD3B	CKD4	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)

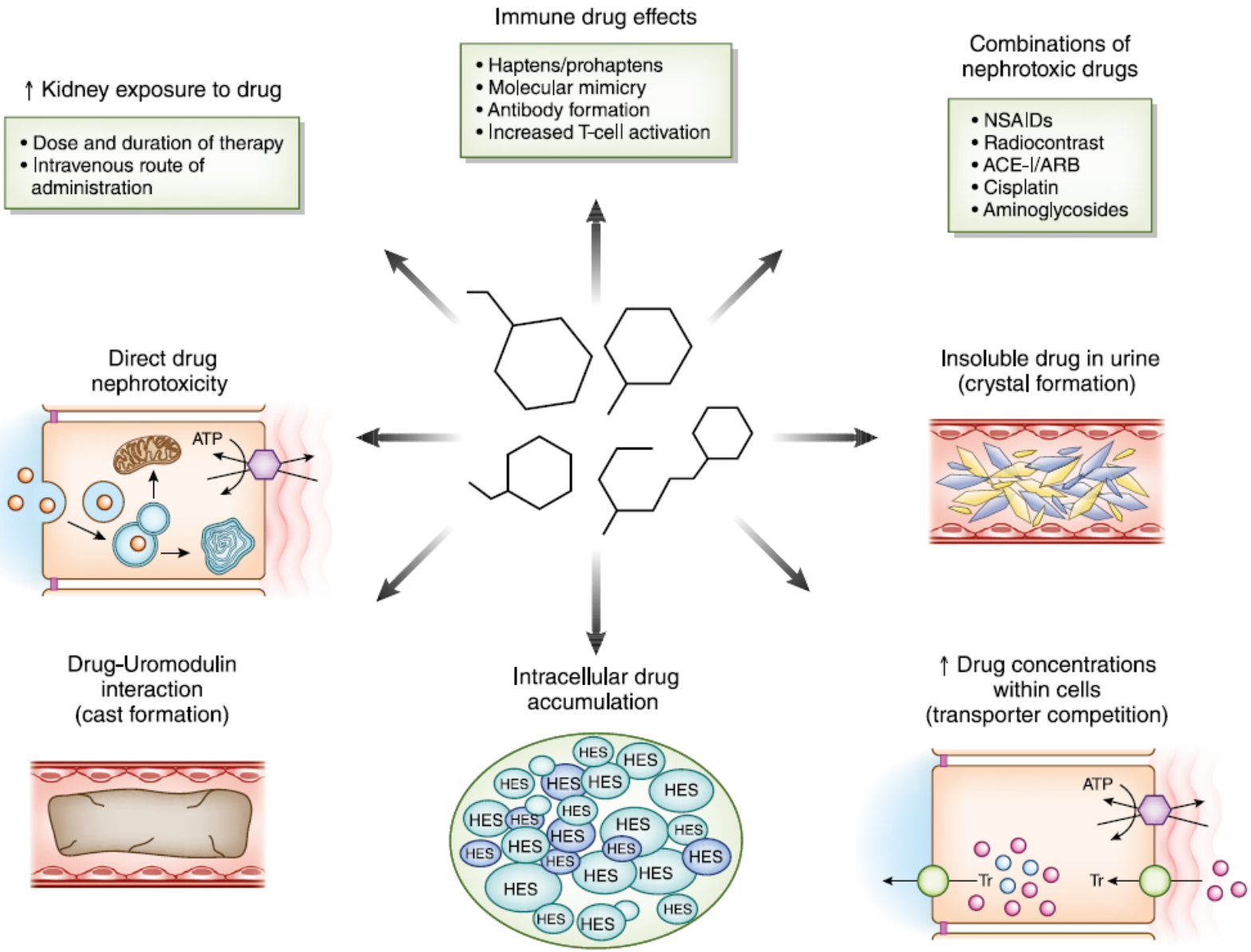
AUC = area under curve,
Cavss= concentration average at steady state

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

WHAT ABOUT IN ESRD PATIENTS ??

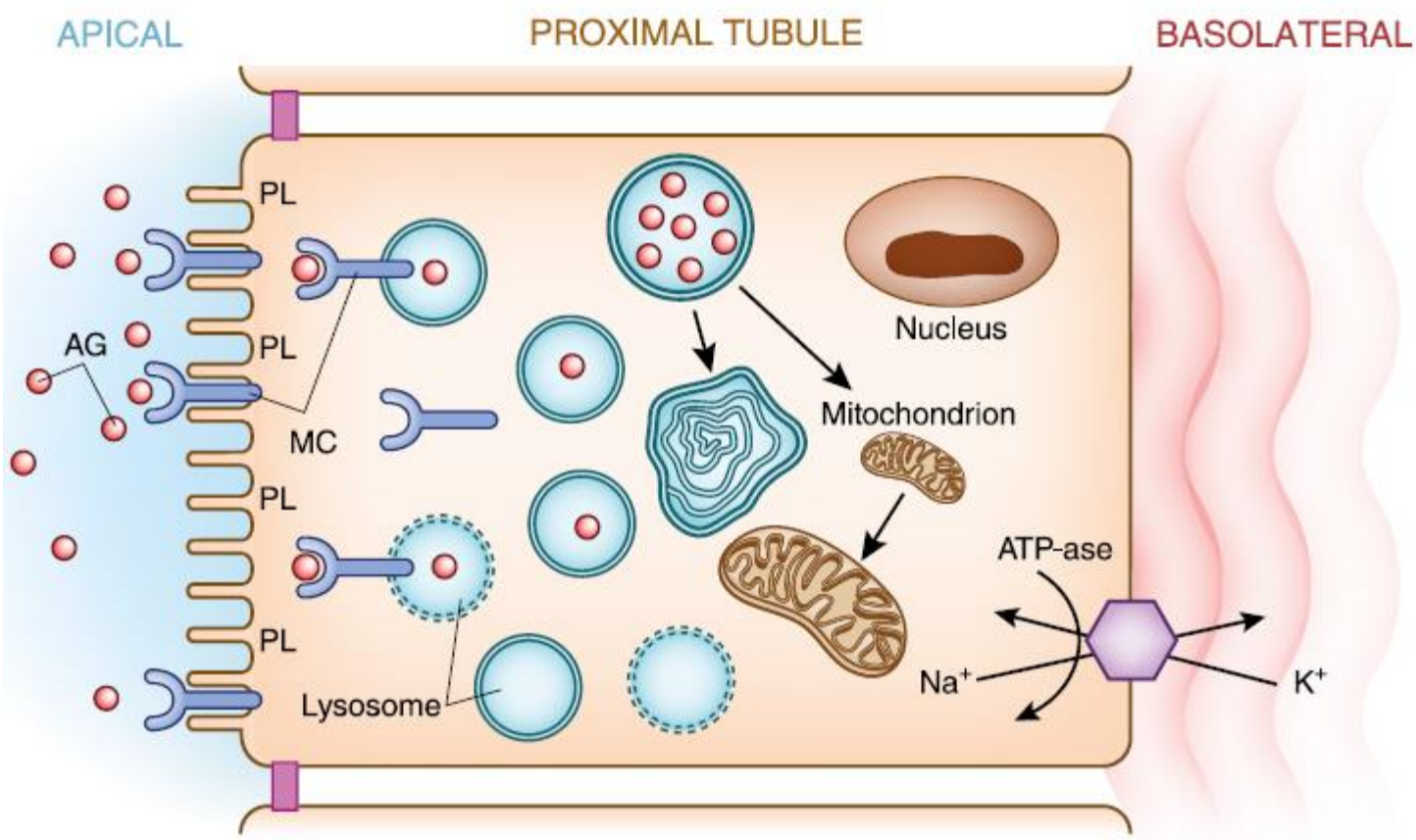
- On **intermittent hemodialysis** (HD): possible extraction of a drug due to high-flux membrane ⟹ compare pre- and post-HD plasma concentrations and in the dialysate !
- Usually, an supplementary dose is given at the end of each HD session (cf. vancomycin); PK studies may be recommended during the intradialytic period (cf. antibiotics such as ceftazidime, meronem…)
- *In case of a drug with high protein binding, large volume of distribution, high non-renal clearance, no significant effect of HD is expected*
- No systematic extrapolation to continuous RRT such as peritoneal dialysis and CVVH(D) !!

4. Drug factors associated with increased risk for nephrotoxicity



Perazella M.A. CJASN (2018)

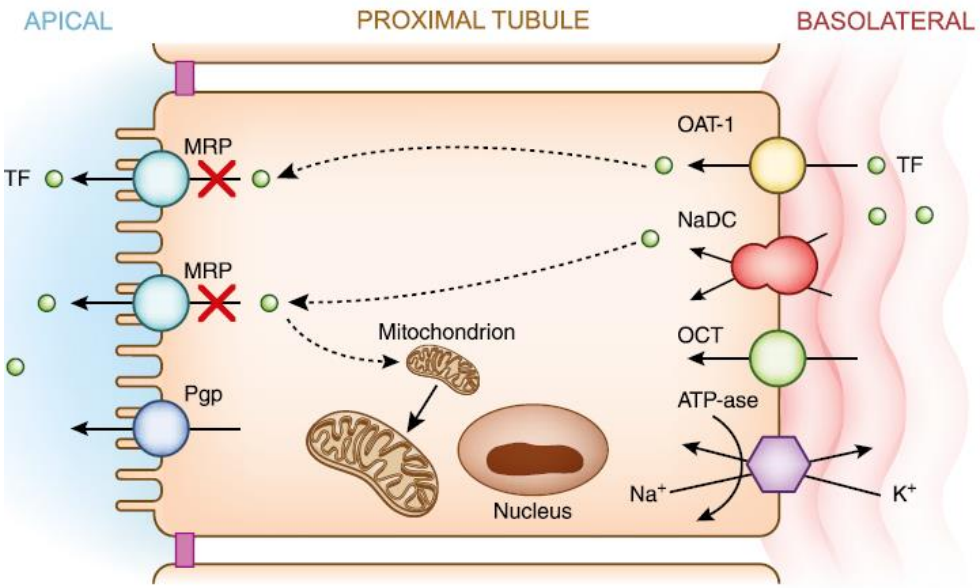
Apical transport of drugs: example of possible cell injury by aminoglycosides



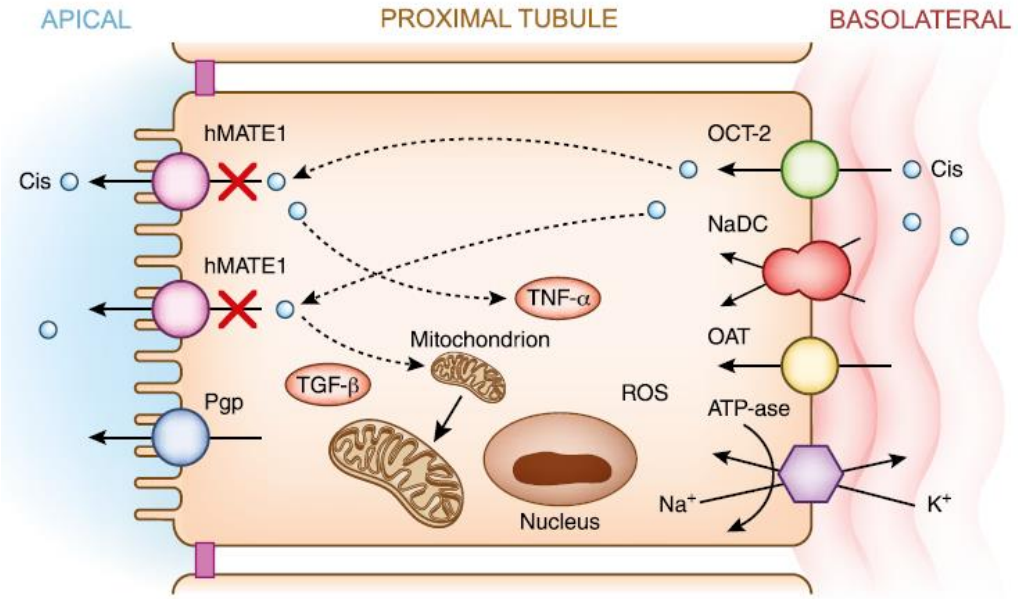
AG: polycationic aminoglycosides
PL: anionic phospholipid membrane
MC: megalin-cubilin

Perazella M.A. CJASN (2018)

Basolateral transport of drugs: possible cell injury by…



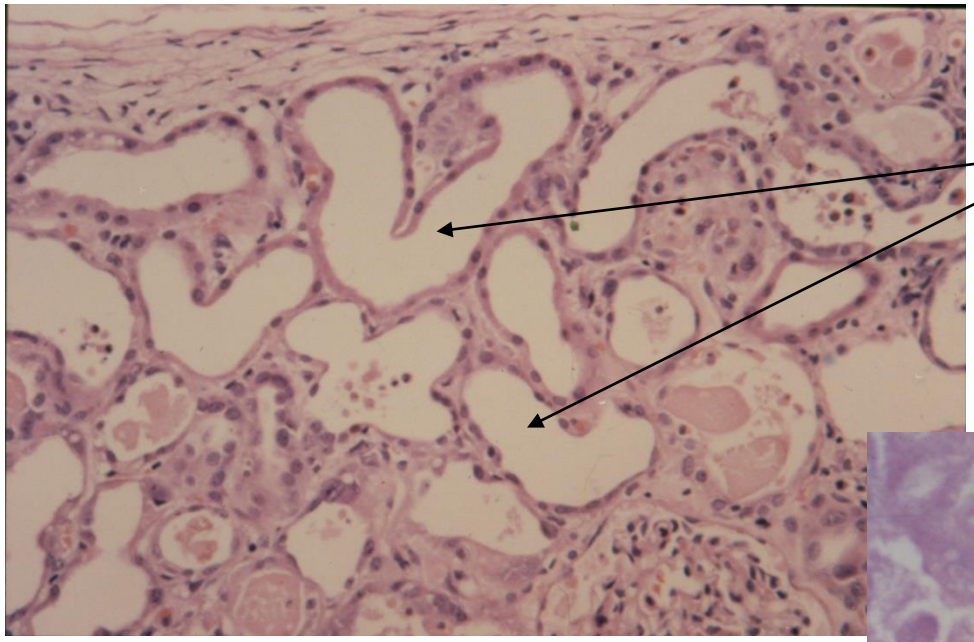
TF: **tenofovir**
OAT-1: organic anion transporter-1
MRP: multidrug resistance protein transporter



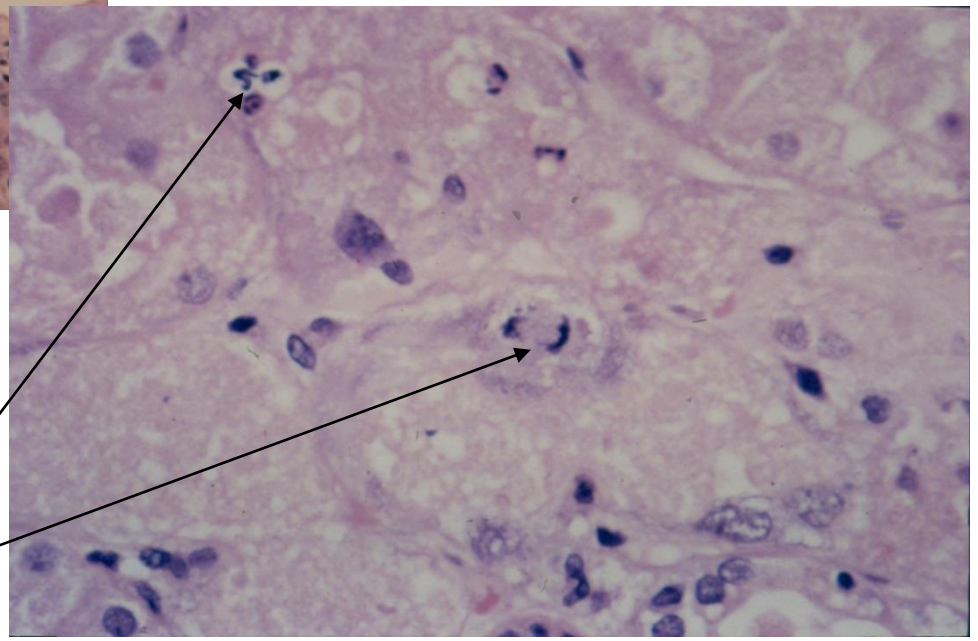
Cis: **cisplatin**
OCT-2: organic cation transporter-2
hMATE1: human multidrug and toxin extrusion protein transporter
Pgp: P-glycoprotein transporter

Perazella M.A. CJASN (2018)

CISPLATIN NEPHROTOXICITY



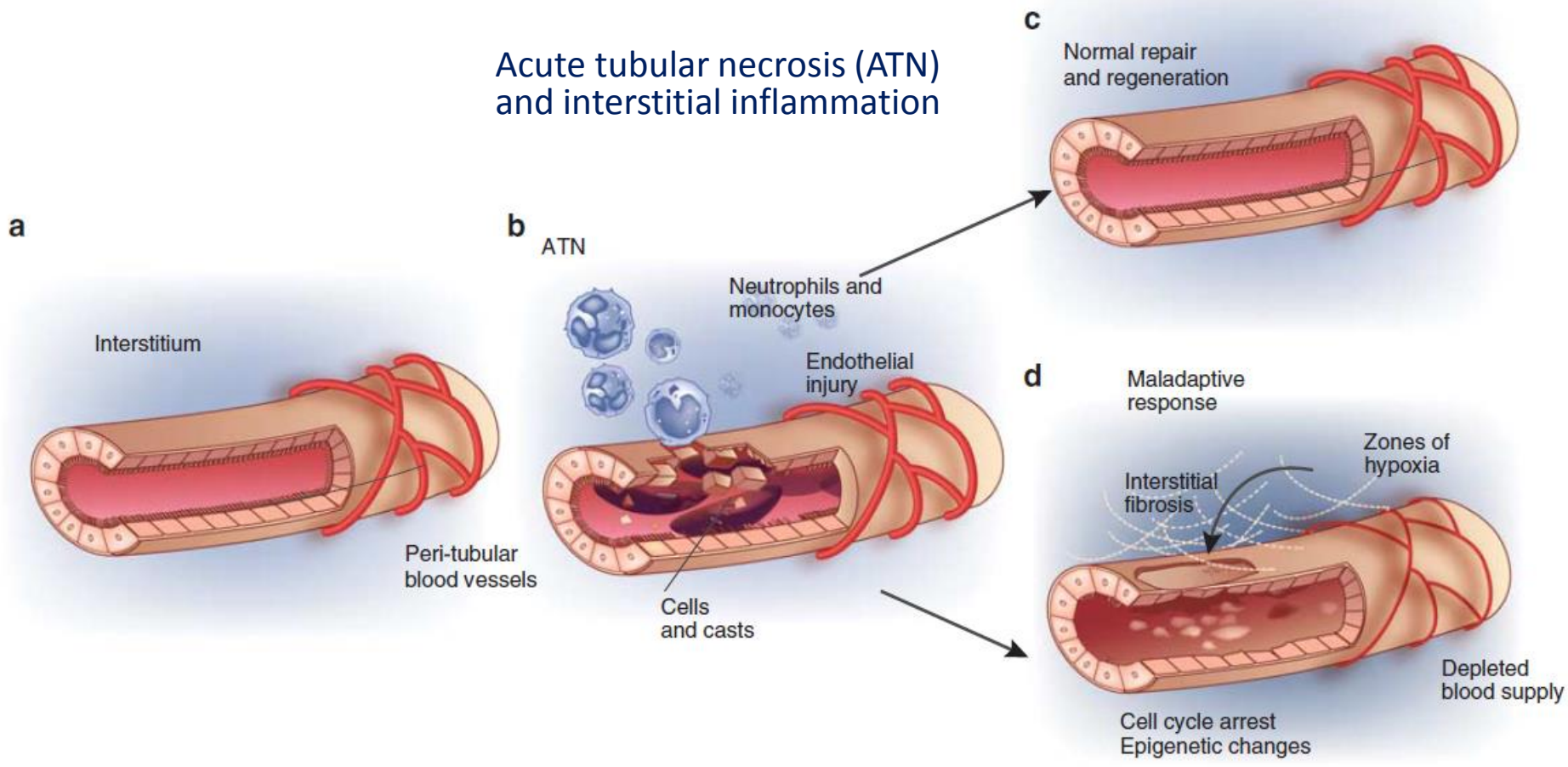
Acute tubular necrosis



Signs of tubular regeneration

Progression of Acute Kidney Injury (AKI) to CKD

Acute tubular necrosis (ATN)
and interstitial inflammation



! Loss of vascular density
! TGF-β promoting fibrosis

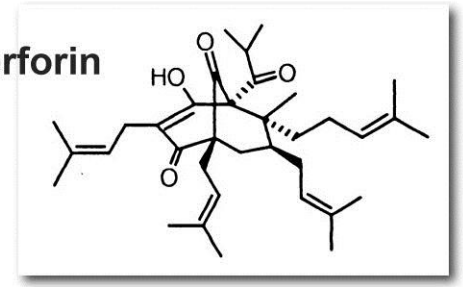
Chawla LS & Kimmel PL. Kidney Int (2012) 82:516-24

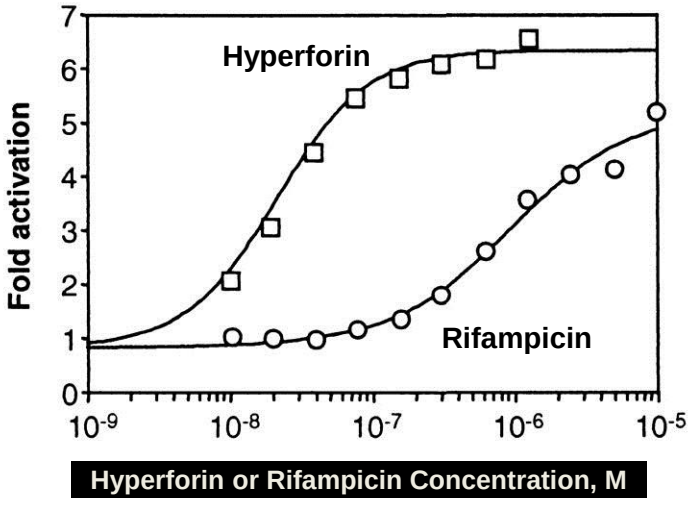
!! WESTERN *AND* EASTERN MEDICINES: UNDERESTIMATED NEPHROTOXICITY !!

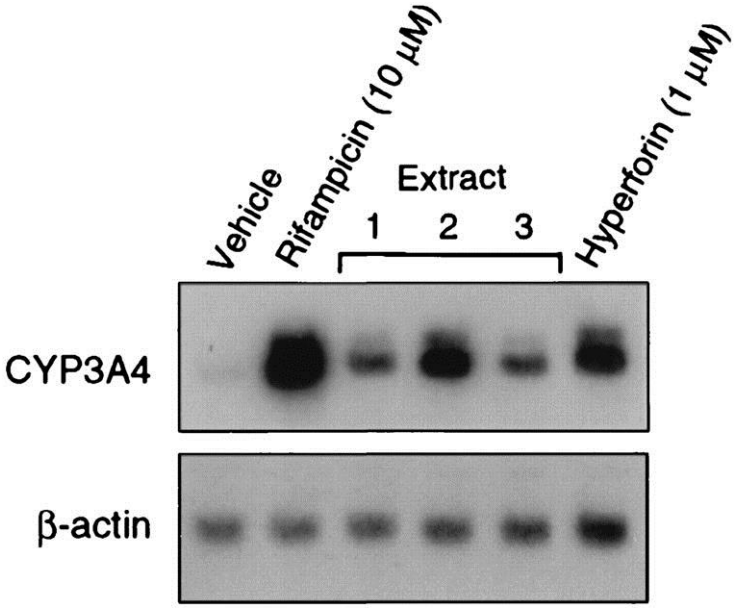
Herb - drug interactions

Hypericum	↓ circulating level of
perforatum	cyclosporin A [CsA]
(St John 's Wort)	and tacrolimus [FK506]
***Panax* sp**	by induction of p450
(ginseng…)	cytochrome (CYP3A4)
Ginkgo biloba	↑ *risk of GI bleed in*
(ginkgo folium)	*combination with ASA or coumadin*

ST. JOHN'S WORT INDUCES HEPATIC DRUG METABOLISM THROUGH ACTIVATION OF THE PREGNANE X RECEPTOR







St. John's wort extracts and hyperforin induce CYP3A4 expression in human hepatocytes.
St Johns wort concentrations:
Extract 1: Nature's Way (9 µg/ml)
Extract 2: Nature's Plus (75 µg/ml)
Extract 3: Solaray (7 µg/ml)

Moore LB et al. PNAS 2000;97:7500

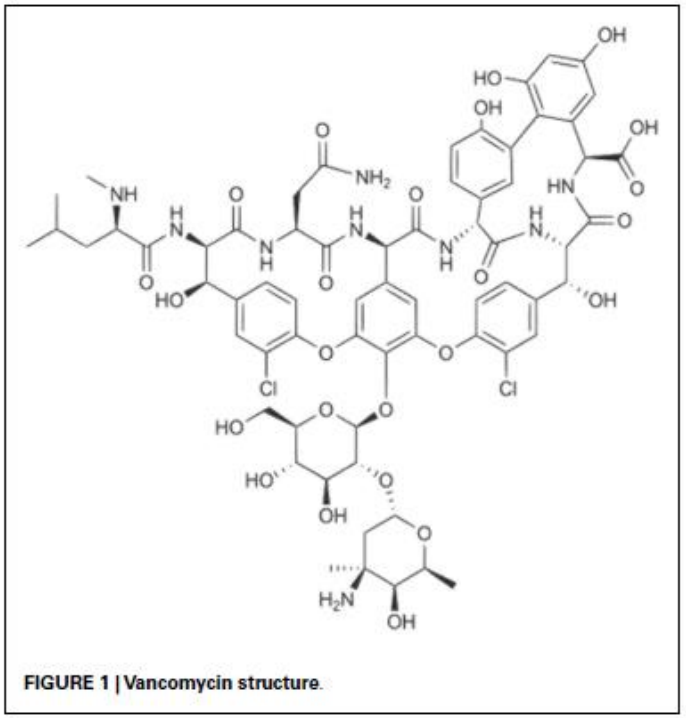


FIGURE 1 | Vancomycin structure.

VANCOMYCIN

= 1st-line agent for methicillin-R coagulase-negative and positive staphylococcal infections

Minimal inhibitory concentration (MIC) against S. aureus ≤ 2 µg/ml

Therapeutic monitoring to avoid toxicity… apparent when serum trough levels > 15 µg/ml

Consensus guidelines (Infectious Dis Soc Am)

Trough concentrations 10-20 mg/l, targeting 15-20 mg/l in severe infections

⟹ ? Toxicity complications ?

VANCOMYCIN-ASSOCIATED NEPHROTOXICITY

Drug - induced

- High trough level
- Daily dose > 4g
- Duration of therapy > 7 days
- *Concomitant* nephrotoxic agents: aminoglycosides, loop diuretics, CsA, ACEI, cisplatine, cyclophosphamide…

Comorbid conditions

Acute kidney injury (AKI)

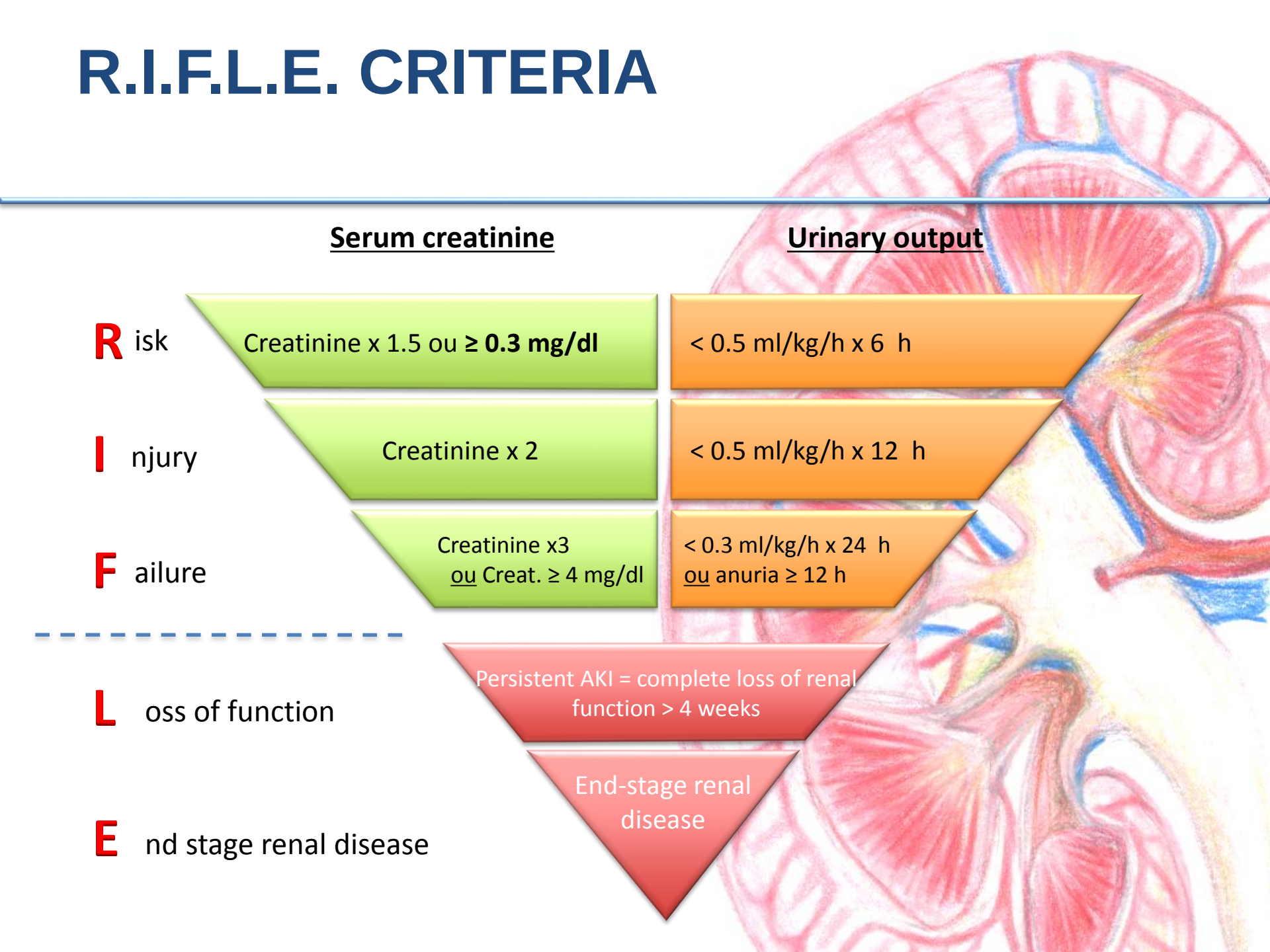
- Impaired GFR within 2-3 days
- ↗ SCrea ≥ 0.5 mg/dl [0.3 mg/dl]
  or
  25 or 50% ↗ in SCrea
- Oliguria (AKI Network)

Diagnosis based upon a marker of *disturbed function* rather than a marker of injury

DEFINITIONS OF AKI

- Rapid decrease in glomerular filtration (several hours to several weeks) followed by a retention of waste products
- Oliguria is frequent (urinary output < 400 ml/day) but not mandatory
- Anuria if urinary output < 100 ml/day
- Initial renal function may be normal or already altered

R.I.F.L.E. CRITERIA



CRITERIA FOR RRT INITIATION

Commonly encountered indications

- Volume overload with severe respiratory or cardiac symptoms
- Non obstructive oliguria (urinary output < 200 ml/12h) or anuria
- Creatinine clearance < 10 ml/min
- Severe hyperkaliemia (K+ $\geq$ 6.5 mEq/l or rapid increase)
- Severe acidemia (pH $\leq$ 7.1-7.2) due to metabolic acidosis
- Prolonged azotemia (BUN $\geq$ 76-100 mg/dl, > 1-2 days without evidence of renal recovery)

> 1 sufficient to initiate RRT, > 2 urgent RRT

Adapted from Bellomo R., Ronco CS. Kidney Int 1998; Atlas of hemofiltration 2001

Can J Hosp Pharm. 2014;67:126-32

Identification of Risk Factors for Nephrotoxicity in Patients Receiving Extended-Duration, High-Trough Vancomycin Therapy

Claire Contreiras, Michael Legal, Tim T Y Lau, Rosanne Thalakada, Stephen Shalansky, and Mary H H Ensom

- 176 patients with high trough levels
- General medicine units of 2 major teaching hospitals
- Retrospective analysis
- Specific risk factors related to VAN

Table 1. Demographic Characteristics of Patients

Characteristic	Value for Study Population (*n* = 176)
Sex, no. (%) male	119 (68)
Age (years), mean ± SD	57.8 ± 17.7
Weight (kg), mean ± SD	73.1 ± 17.1
Vancomycin dose (mg/day), median (IQR)	2000 (1500–2500)
Baseline SCr (μmol/L), mean ± SD	84.6 ± 38.6
Baseline CrCl (mL/min), mean ± SD	100.8 ± 48.8
Length of stay (days), median (IQR)	26 (17–48)
Length of treatment (days), median (IQR)	15 (11–23)
Length of treatment (weeks), median (IQR)	3 (2–4)
Clinical area medicine, no. (%) of patients	84 (48)
Concurrent receipt of nephrotoxins,* no. (%) of patients	113 (64)
Experienced nephrotoxicity, no. (%)	24 (14)

CrCl = creatinine clearance, IQR = interquartile range, SCr = serum creatinine, SD = standard deviation.

*Common nephrotoxins are nonsteriodal anti-inflammatory drgus, diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, radiocontrast dye.

Table 2. Clinical Course of Nephrotoxicity

Variable	Value
Peak SCr (μmol/L), mean ± SD	134.5 ± 53.4
Time to first rise in SCr from start of therapy (days), median (IQR)	14 (10–21)
Time to peak SCr from start of therapy (days), median (IQR)	15 (12–23)
Time to resolution from peak SCr (days), median (IQR)	7 (4–9)
RIFLE category, no. (%) of patients*	
Risk	17 (70.8)
Injury	3 (12.5)
Failure	1 (4.2)
SCr increase ≥ 26.4 μmol/L, no. (%) of patients	3 (2.5)

IQR = interquartile range, SCr = serum creatinine, SD = standard deviation.
*Among patients with nephrotoxicity.

Table 3. Univariate Analysis for Nephrotoxicity

Variable	Nephrotoxicity: Yes (*n* = 24)	Nephrotoxicity: No (*n* = 152)	*p* value
Age (years), mean ± SD	60 ± 19	57 ± 17	0.43
Weight (kg), mean ± SD	74.5 ± 17.6	72.9 ± 17.1	0.68
Baseline CrCl (mL/min), mean ± SD	103.3 ± 49	100.4 ± 48.9	0.79
Baseline SCr* (μmol/L), mean ± SD	84.6 ± 43.1	84.5 ± 38	> 0.99
Duration of vancomycin treatment, mean ± SD			
In days	24.8 ± 16.1	17.5 ± 10.3	0.044
In weeks*	3.8 ± 2.2	2.9 ± 1.3	0.080
Clinical area, no. (%) of patients			
Medicine*	16 (67)	68 (45)	0.046
ICU	2 (8)	14 (9)	0.90
Type of infection treated, no. (%) of patients			
Osteomyelitis or septic arthritis	5 (21)	32 (21)	0.90
Pneumonia	5 (21)	19 (12)	0.31
Febrile neutropenia†	2 (8)	2 (1)	0.032
Organisms identified, no. (%) of patients			
MRSA	12 (48)	78 (51)	0.76
MSSA†	2 (8)	2 (1)	0.032
Enterococcus	3 (12)	10 (7)	0.34
Comorbidity, no. (%) of patients			
Diabetes mellitus	6 (25)	30 (20)	0.62
Hypertension	9 (38)	49 (32)	0.71
Gastrointestinal comorbidity	6 (25)	16 (11)	0.056
Malignancy	6 (25)	15 (10)	0.044
HIV infection	0 (0)	20 (13)	0.059
Sepsis	0 (0)	20 (13)	0.059
Concurrent nephrotoxin, no. (%) of patients			
Any	11 (46)	102 (67)	0.043
ACE inhibitor or ARB*	1 (4)	36 (24)	0.029
IV contrast dye†	2 (8)	40 (26)	0.054
NSAID	1 (4)	25 (16)	0.10

ACE = angiotensin-converting enzyme, ARB = angiotensin receptor blocker, CrCl = creatinine clearance, ICU = intensive care unit, MRSA = methicillin-resistant *Staphylococcus aureus*, MSSA = methicillin-sensitive *Staphylococcus aureus*, NSAID = nonsteroidal anti-inflammatory drug, SCr = serum creatinine, SD = standard deviation.

*Variables included in multivariate logistic regression.

†Excluded from multivariate logistic regression (even though $p < 0.1$) because of the small number of patients affected.

Table 4. Predictors of Vancomycin-Associated Nephrotoxicity by Multivariate Analysis*

Parameter	Adjusted OR (95% CI)	*p* value
Clinical area general medicine	2.57 (1.01–6.58)	0.048
Duration of vancomycin treatment (weeks)	1.35 (1.04–1.76)	0.025
Concurrent use of ACE inhibitor or ARB	0.13 (0.02–1.00)	0.049

ACE = angiotensin-converting-enzyme, ARB = angiotensin receptor blocker, CI = confidence interval, OR = odds ratio.

*Variables in the multivariate analysis were controlled for baseline serum creatinine.

Pharmacotherapy 2014;34:662-69

Comparison of Acute Kidney Injury During Treatment with Vancomycin in Combination with Piperacillin-Tazobactam or Cefepime

Diane M. Gomes,[1] Carmen Smotherman,[2] Amy Birch,[1,3] Lori Dupree,[1,3] Bethany J. Della Vecchia,[1,3] Dale F. Kraemer,[2,4] and Christopher A. Jankowski[1,3]*

[1]UF Health Jacksonville, Jacksonville, Florida; [2]Center for Health Equity and Quality Research, Jacksonville, Florida; [3]University of Florida College of Pharmacy, Jacksonville, Florida; [4]Department of Neurology, University of Florida, Jacksonville, Florida

- Retrospective matched cohort
- 224 patients without preexisting renal dysfunction and receiving antimicrobial combination

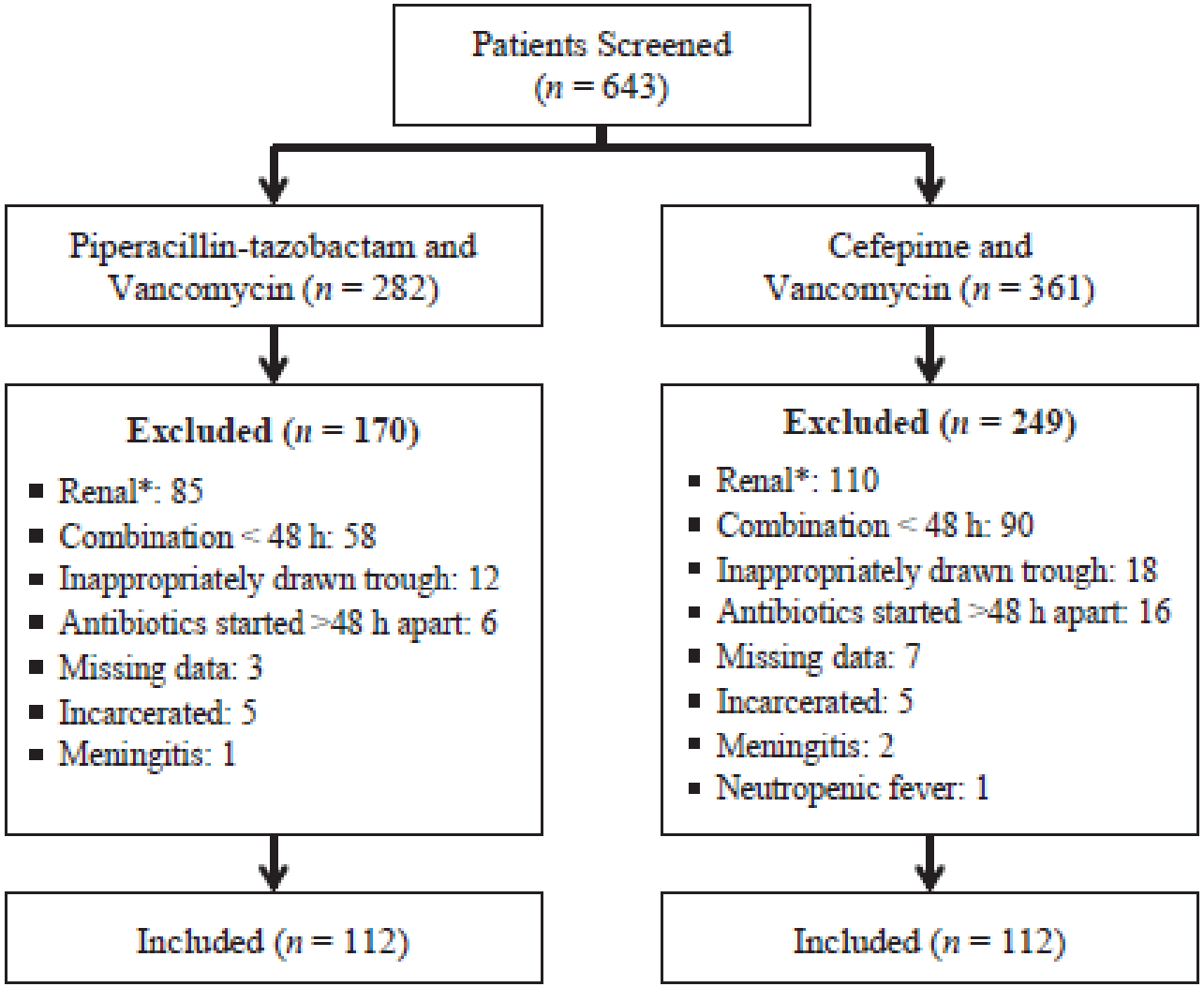


Figure 1. Study design. *Receiving dialysis, documented history of chronic kidney disease (≥ Stage III), structural kidney disease (e.g. one kidney, kidney transplant, kidney tumor), documented renal insufficiency (Cl_{cr} < 60 mL/min)

Table 2. Prevalence and duration of acute kidney injury (AKI) (unmatched data)

34.8 % vs 12.5 %

	TZP-VAN (n=39)	FEP-VAN (n=14)	p
Highest VAN trough prior to AKI, mg/L	22.6	24.3	0.52[a]
In ICU at AKI onset, no. (%)	11 (28.2)	9 (64.3)	0.017[b]
Days to AKI from combination start, mean	4.97 ± 3.1	4.85 ± 2.9	0.975[a]
AKIN stage, no. (%)			
I	25 (64.1)	6 (42.9)	0.049[c]
II	3 (7.7)	5 (35.7)	
III	11 (28.2)	3 (21.4)	
Total days of AKI, mean	7.6 ± 6.8	10.6 ± 14.8	0.626[a]
Outcome of AKI at discharge			
Resolved, no. (%)	16 (41.0)	3 (21.4)	0.190[c]
Insult still present, no. (%)	23 (59.0)	11 (78.6)	
Dialysis required, no. (%)	0 (0.0)	1 (7.1)	1.00[c]
Renal consult, no. (%)	6 (15.4)	4 (28.6)	0.426[c]

AKI = acute kidney injury; AKIN = Acute Kidney Injury Network; FEP-VAN = cefepime-vancomycin combination; ICU = intensive care unit; TZP-VAN = piperacillin-tazobactam and vancomycin combination.

[a]Wilcoxon rank sum test.

[b]Pearson χ^2 test.

[c]Fisher exact test.

OR of AKI **5.67** for TZP-VAN *vs* FEP-VAN

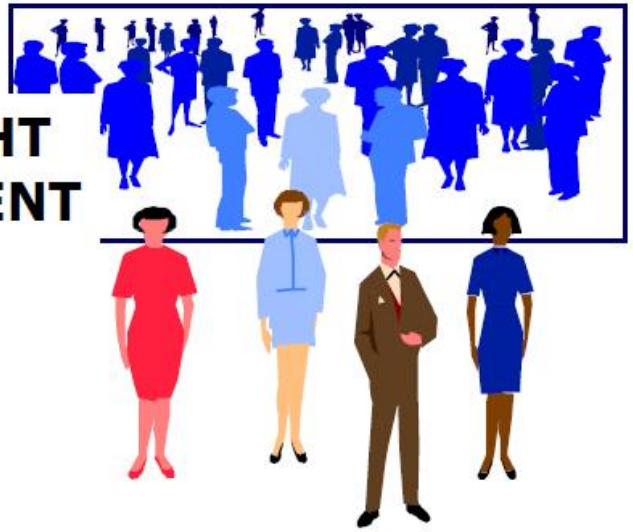
6. TAKE HOME MESSAGES

- CKD and AKI are comorbid conditions requiring adequate staging and care
- AKI to CKD transition is not rare and needs to be prevented if possible
- AKI as well as CKD are risk factors for drug-induced nephrotoxicity
- Drug dosing adjustment is determined after careful kidney function assessment; PK studies are needed in order to focus on efficacy and safety !
- Pay special attention to drug-drug and herb-drug interactions !

The Ultimate Goal:

RIGHT DRUG

RIGHT PATIENT

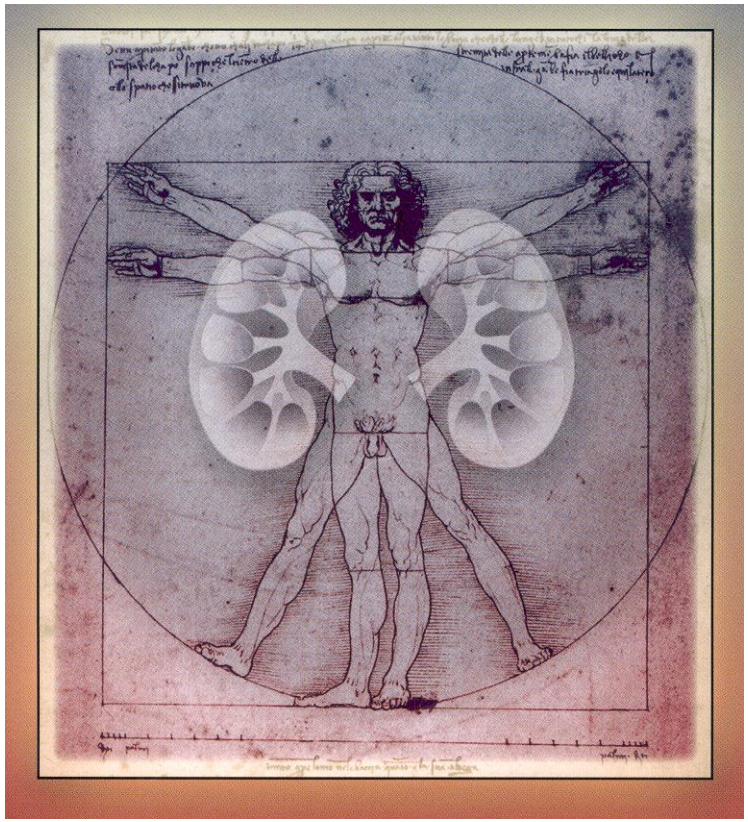


GOAL

RIGHT DOSE

RIGHT TIME

QUESTIONS ??



Thank you !