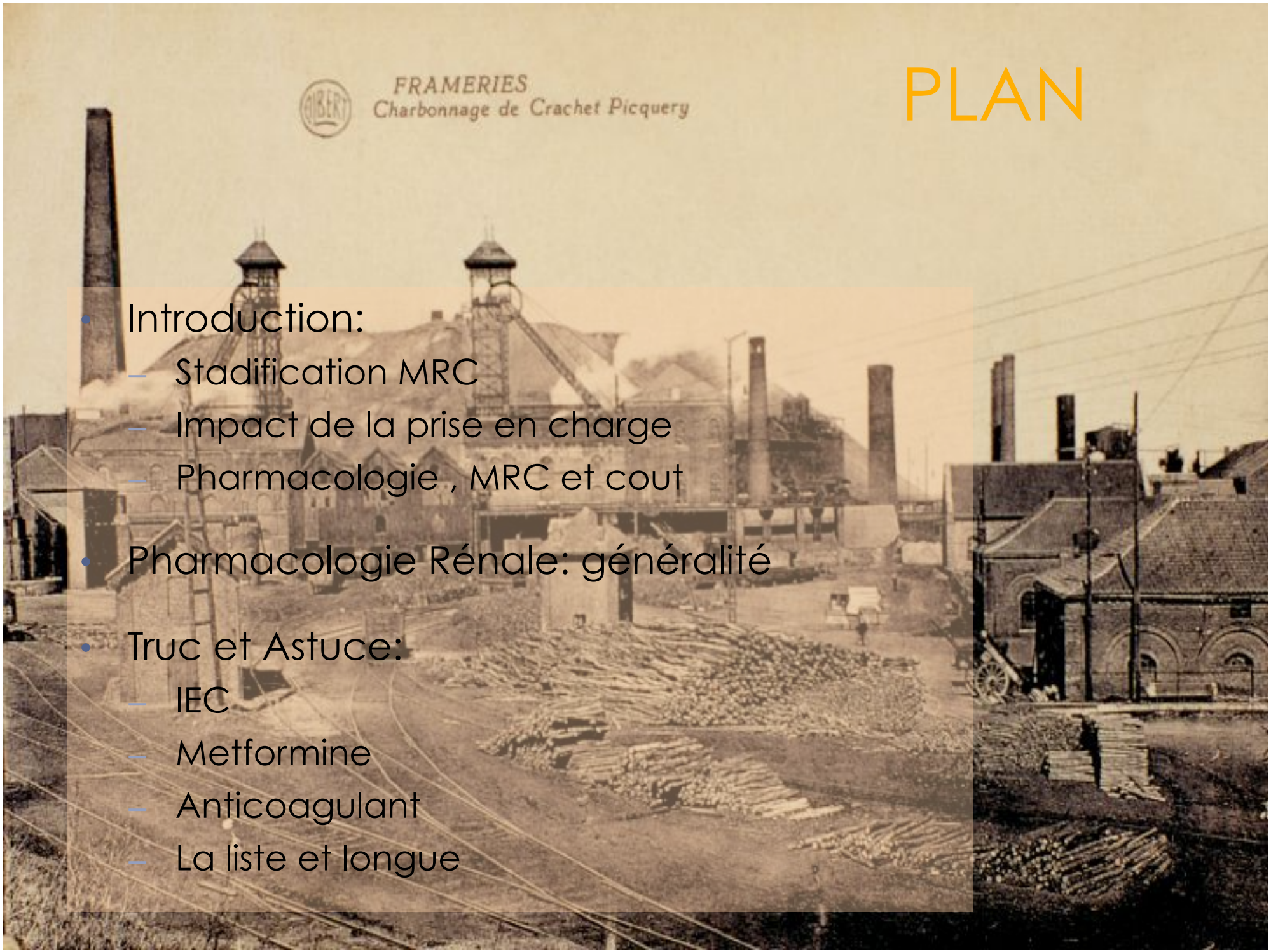
Pharmacologie et maladie rénale chronique

ROYAL UNION MEDICAL BORAINE

Dr Guillen Anaya Miguel Ange
Médecine Interne et Néphrologie



PLAN

- Introduction:
  - Stadification MRC
  - Impact de la prise en charge
  - Pharmacologie , MRC et cout
- Pharmacologie Rénale: généralité
- Truc et Astuce:
  - IEC
  - Metformine
  - Anticoagulant
  - La liste et longue

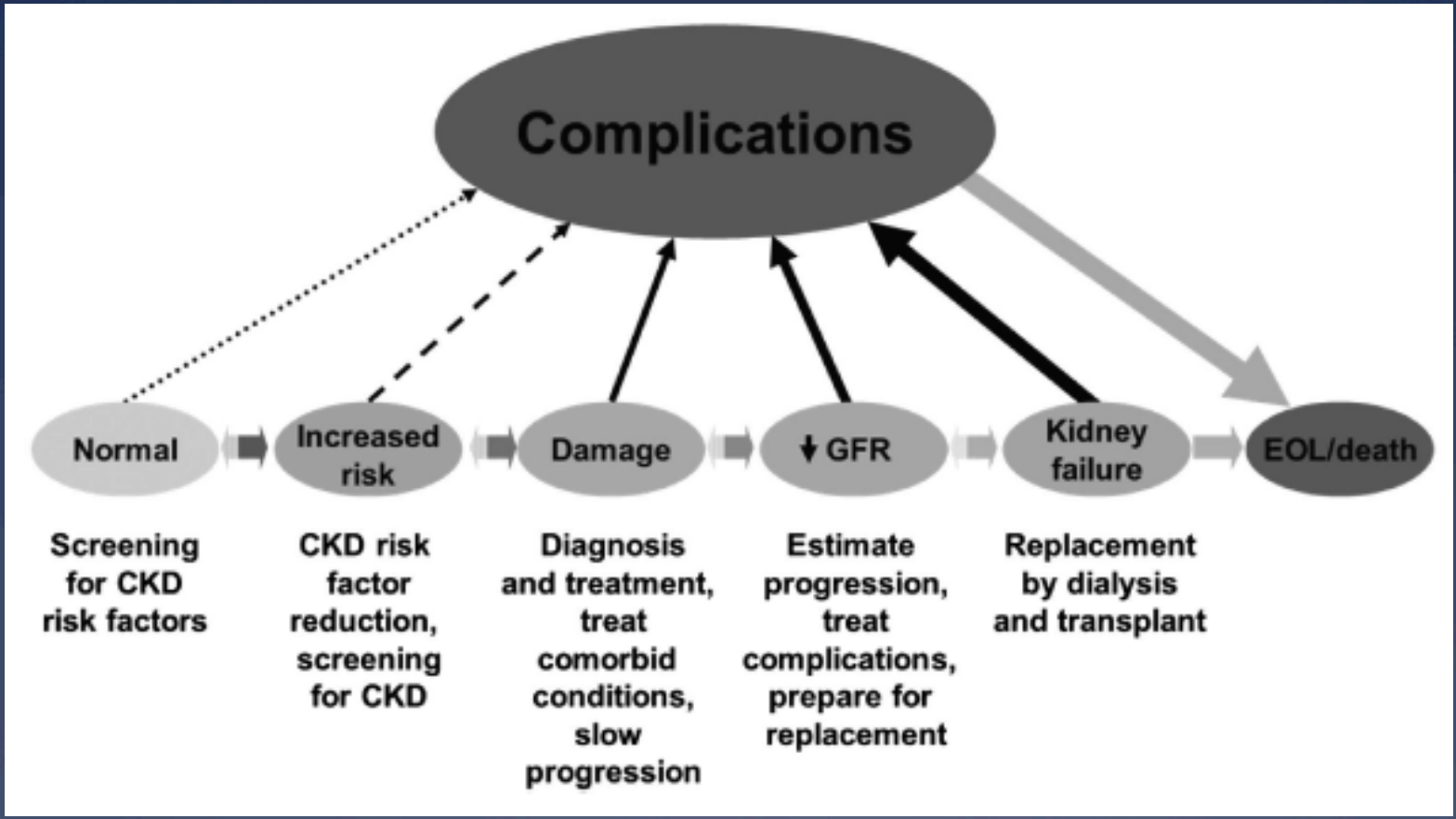
Stadification MRC-CKD KDIGO

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

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			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

Concepte


Complications
Normal
Increased risk
Damage
GFR
Kidney failure
EOL/death
Screening for CKD risk factors
CKD risk factor reduction, screening for CKD
Diagnosis and treatment, treat comorbid conditions, slow progression
Estimate progression, treat complications, prepare for replacement
Replacement by dialysis and transplant

Decline in kidney function before and after nephrology referral and the effect on survival in moderate to advanced chronic kidney disease

Chris Jones1, Paul Roderick1, Scott Harris1 and Mary Rogerson2

Nephrol Dial Transplant (2006) 1 of 11

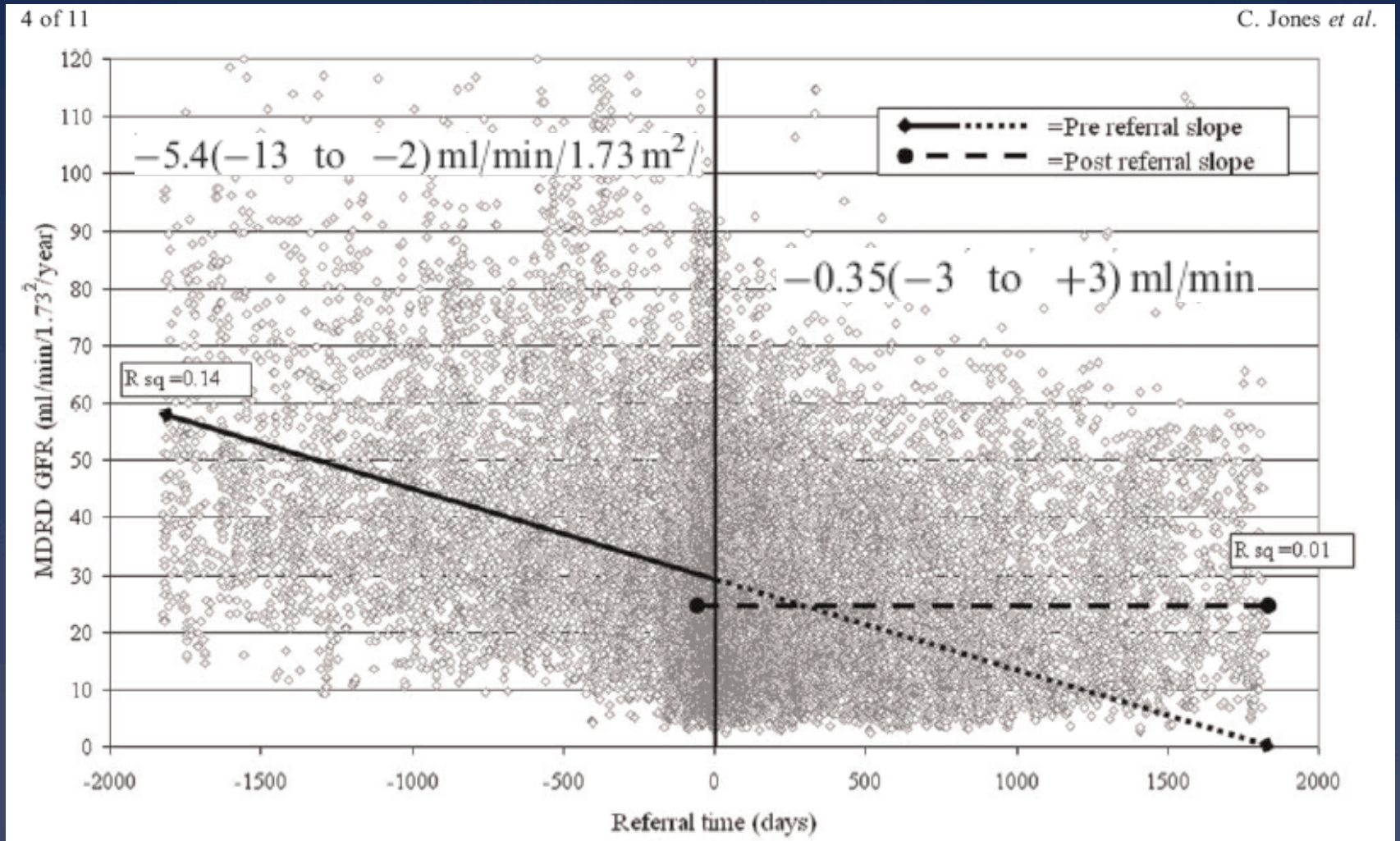


Fig. 1. Decline in MDRD GFR in the 5 years prior to and following nephrology referral with regression lines of summary pre- and post-referral GFR slopes (each point is a single GFR measure).

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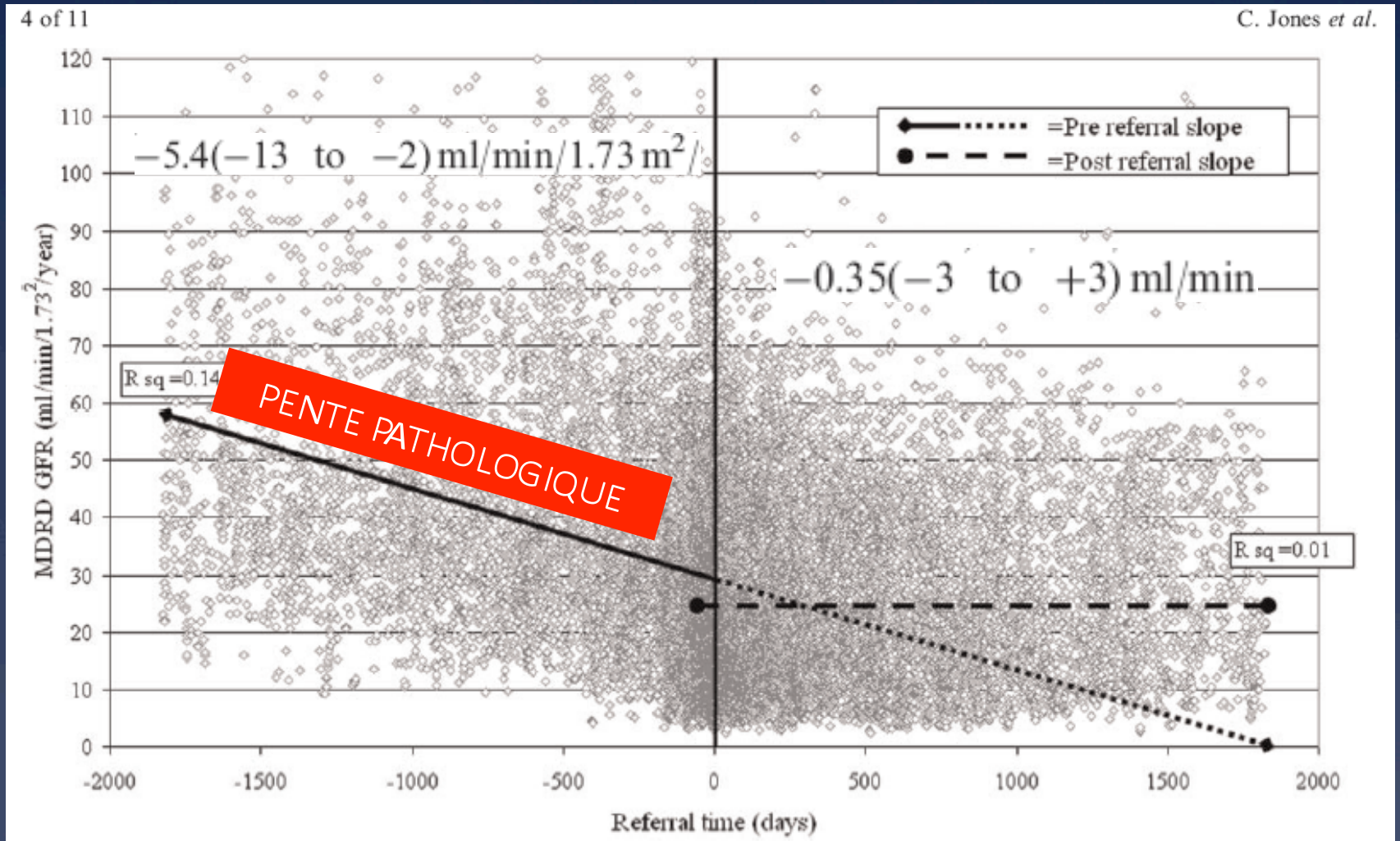

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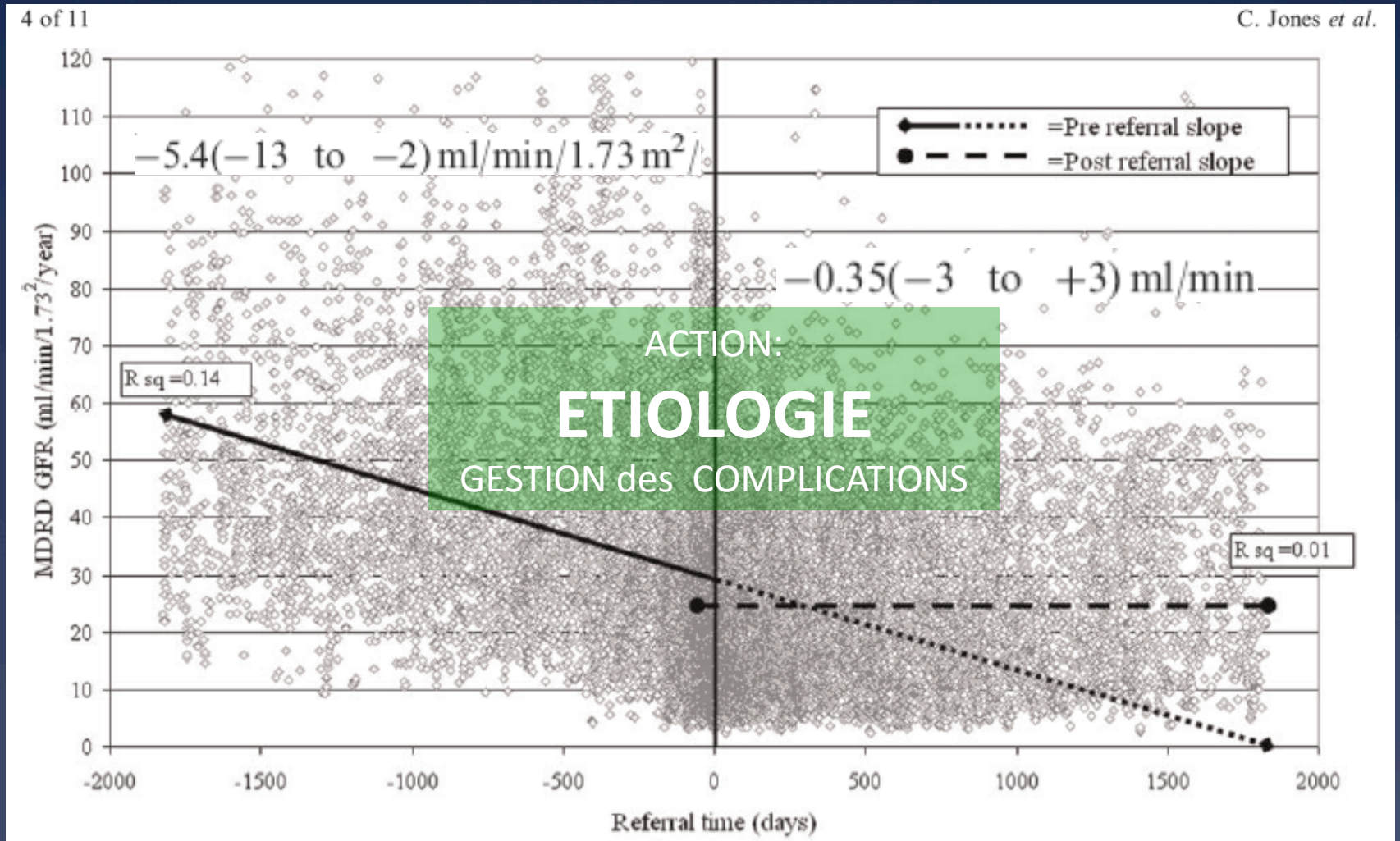

ACTION:

ETIOLOGIE

GESTION des COMPLICATIONS

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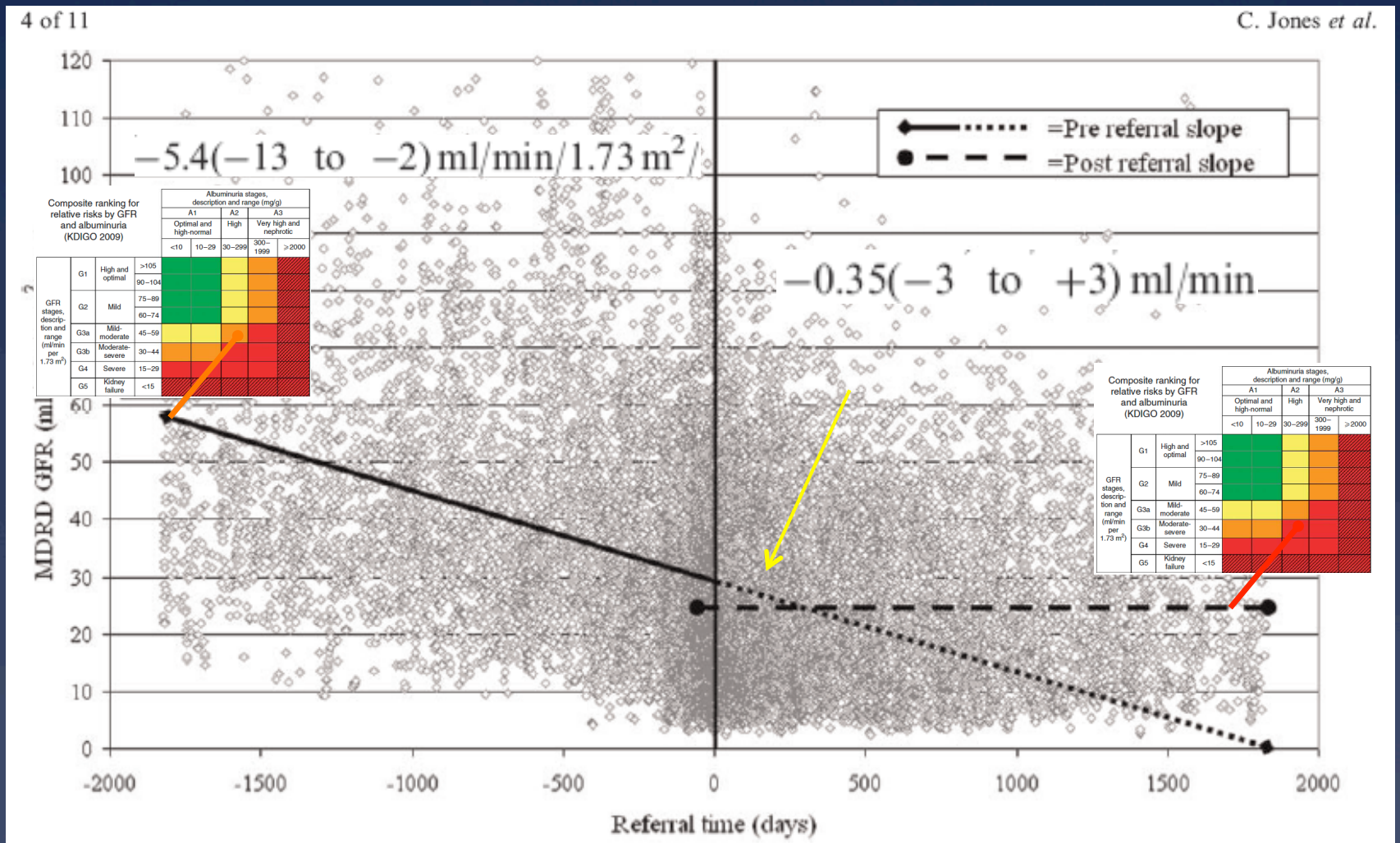
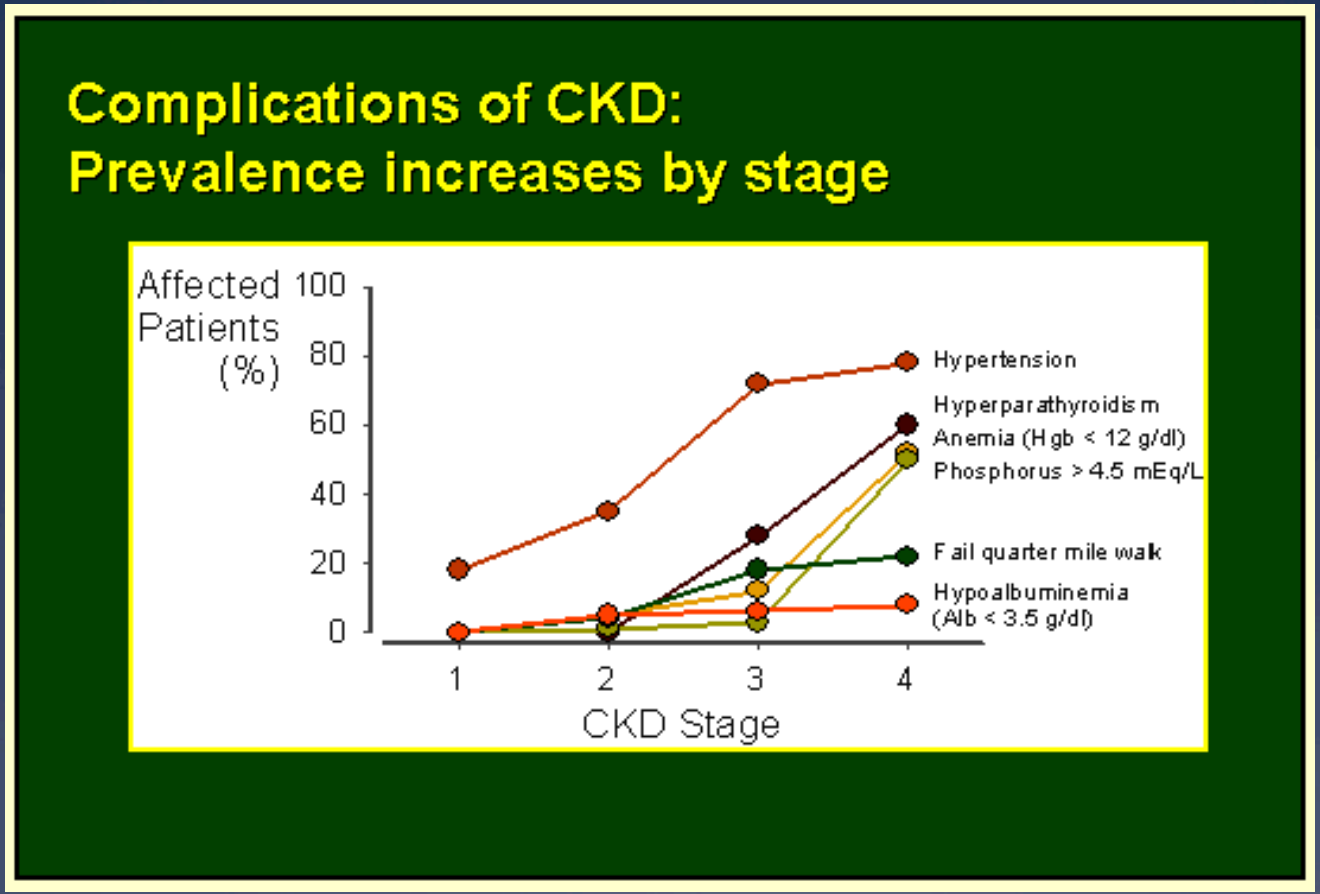
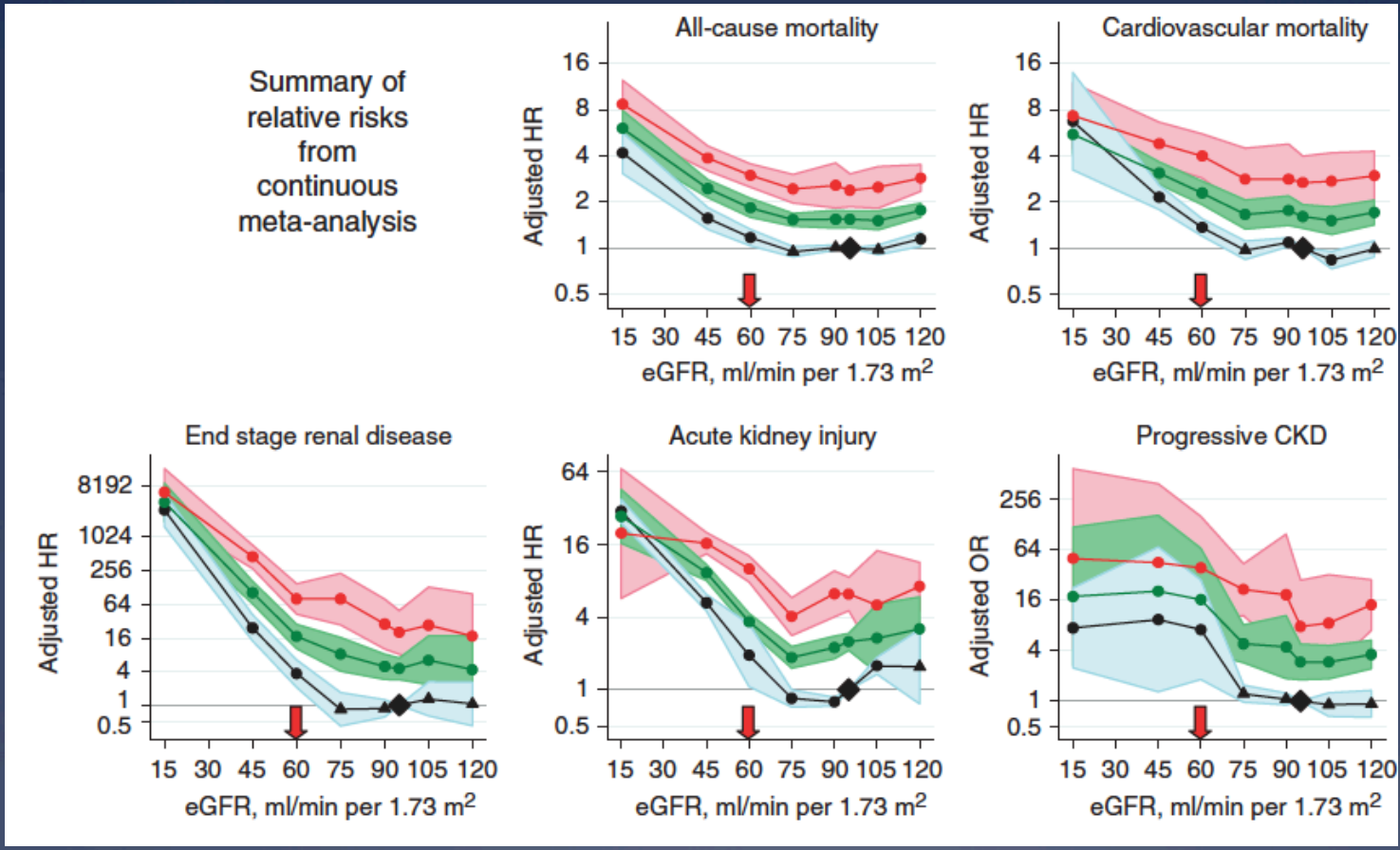


Fig. 1. Decline in MDRD GFR in the 5 years prior to and following nephrology referral with regression lines of summary pre- and post-referral GFR slopes (each point is a single GFR measure).

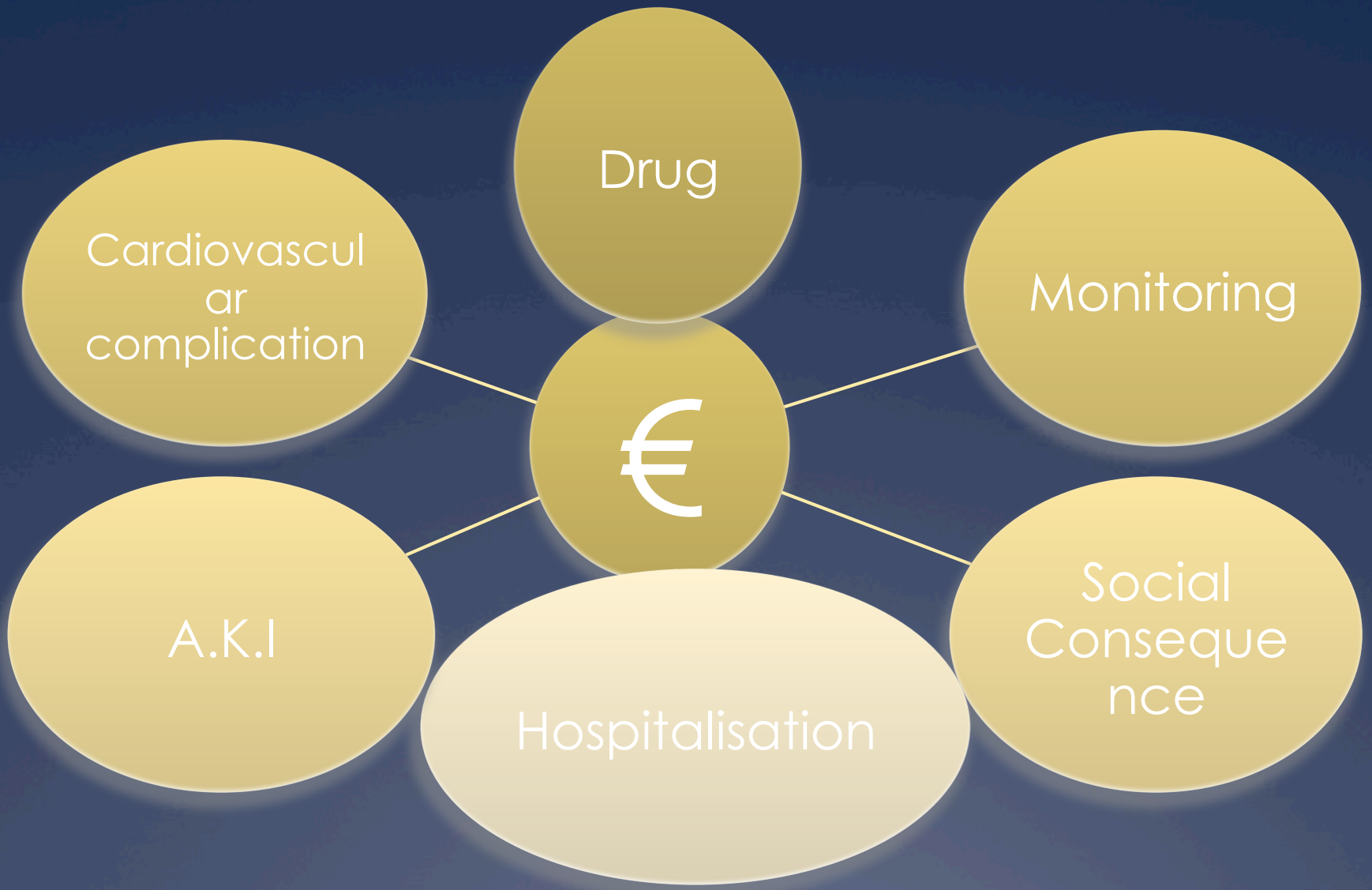
COUTS et COMPLICATIONS

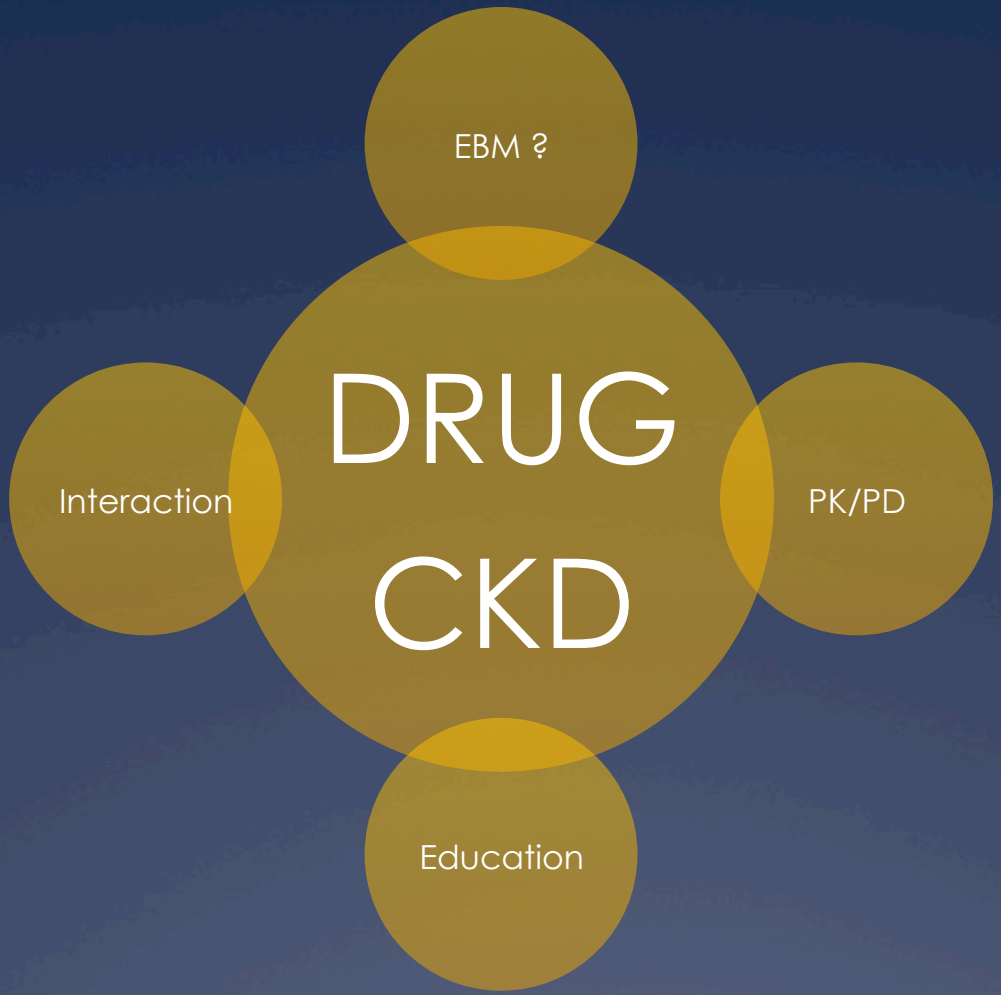


CKD Complication

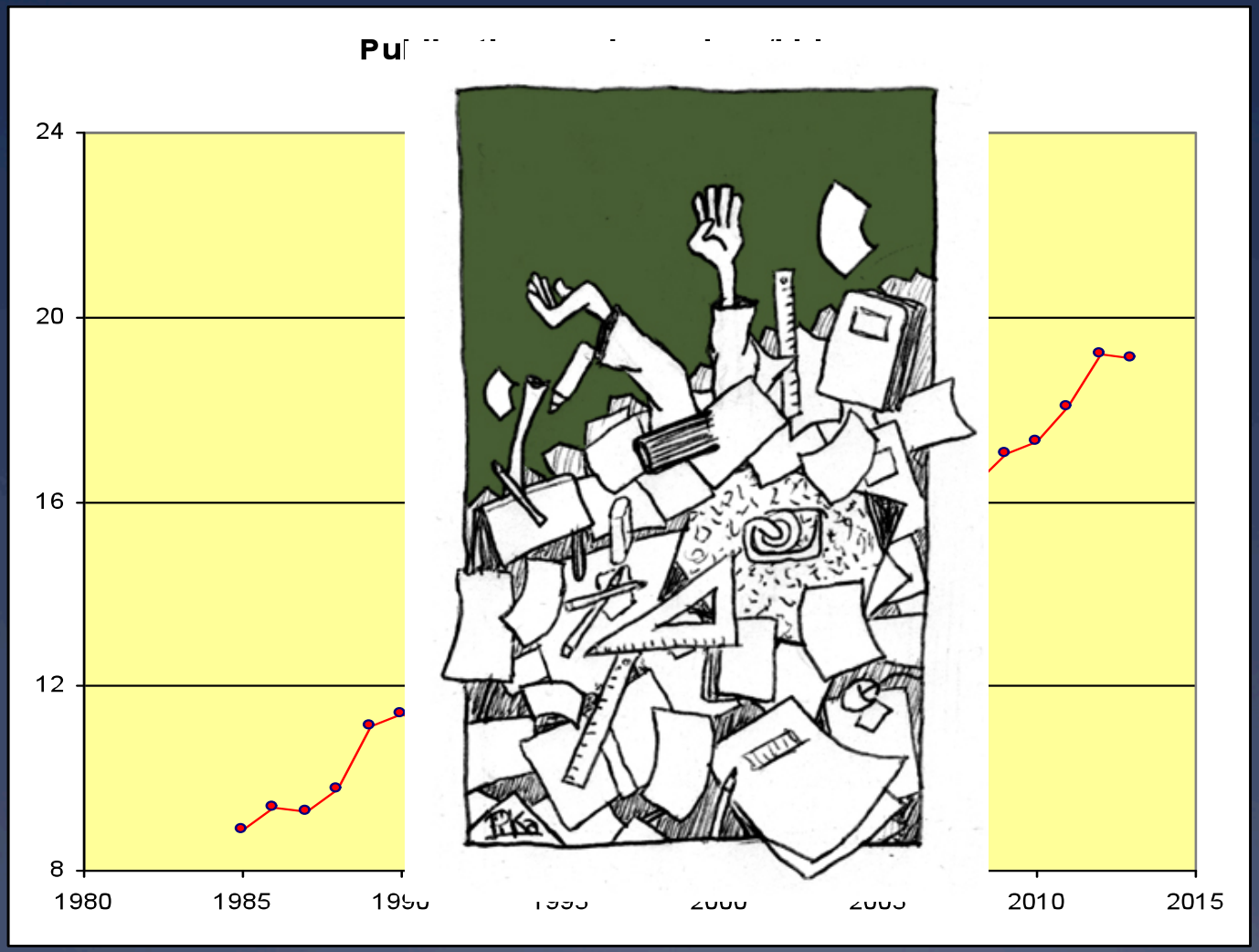


Cost of CKD


Drug
Cardiovascular complication
Monitoring
€
A.K.I
Hospitalisation
Social Consequence


EBM ?
DRUG
CKD
Interaction
PK/PD
Education

Nephro - pharmacologie



ORGANISATION DE BONNE PRATIQUE

KIDNEY DISEASE · IMPROVING GLOBAL OUTCOMES · KDIGO

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

FDA U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Pharmacocinétique et MRC

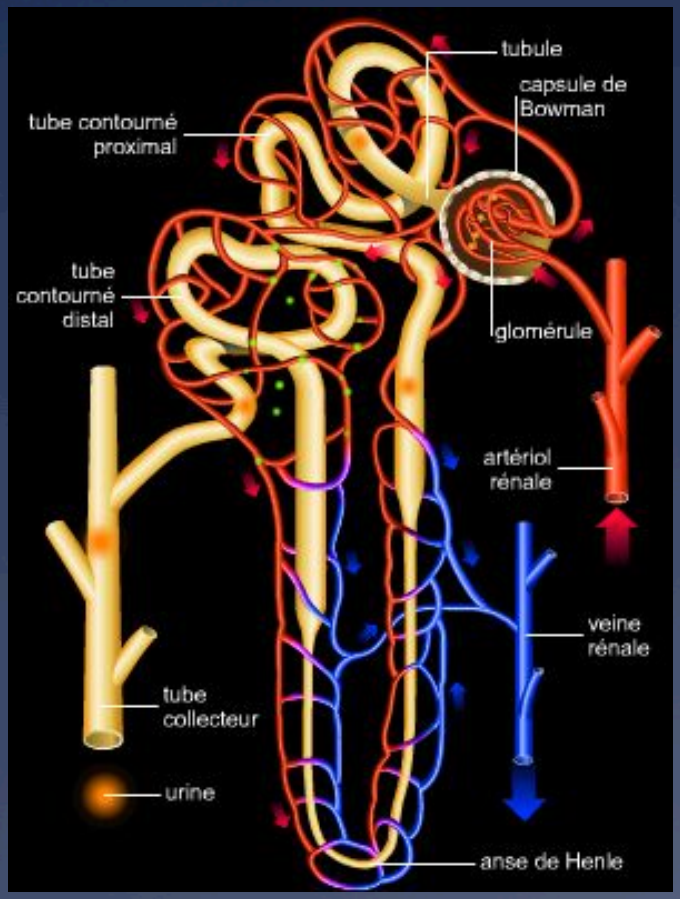
- Pharmacocinétique: étude du devenir d'un médicament dans un organisme.

- La pharmacodynamie clinique permet de définir le meilleur ajustement posologique pour atteindre l'effet du traitement :

Pharmacocinétique et MRC

- Absorption:
  - Diminution du transit intestinal
  - Interaction médication intra intestinale
- Volume de distribution
- Liaison Protéine:
  - Taux d'albumine.
  - Liaison toxine urémique.
- Filtration glomérulaire
- Modification enzymologie extrarénale.
- Modification métabolisme général.

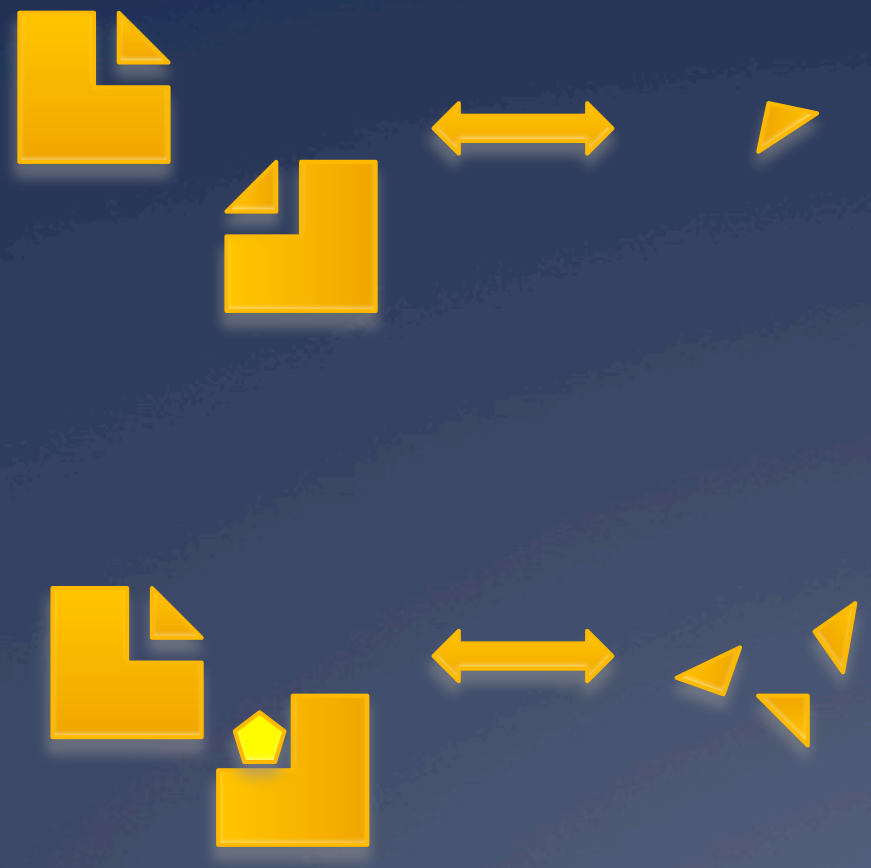
Elimination rénale



- GFR ⬇ = Elimination⬇

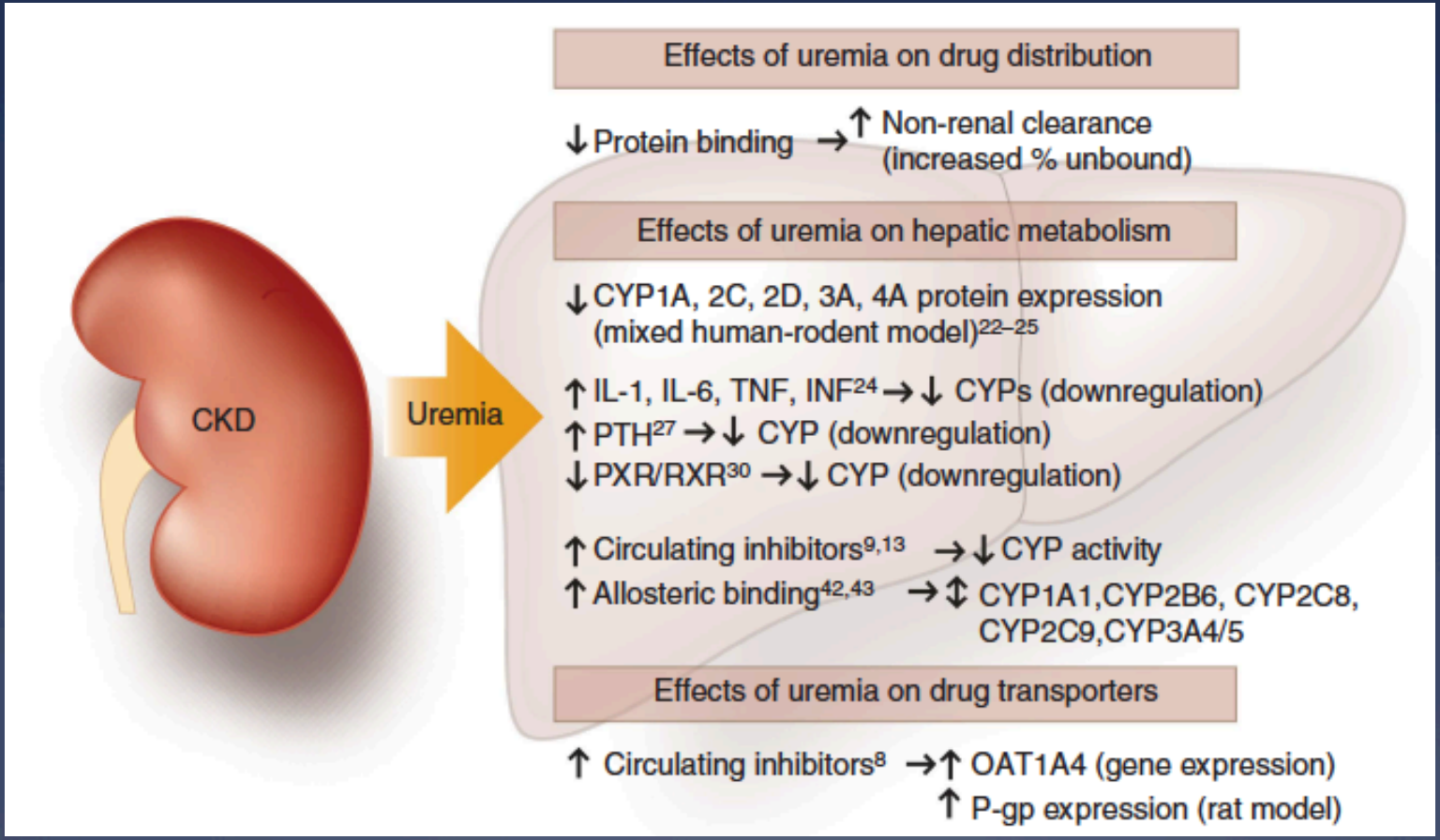
- Métabolite actif
- Interaction non rénale
- AINS.
- Déshydratation.

Liaison Albumine



* Chez le sujet urémique la liaison à l'albumine est diminué par la présence de toxine urémique liée à l'albumine. A défaut de dosage de la fraction libre il convient de viser des taux plus bas.

METABOLISME HEPATIQUE



Effects of chronic kidney disease on hepatic drug metabolism and transport . mini review CK Yeung et al.KI 2014 85 522 528

TOXICITE MEDICAMENTEUSE

- Rénale Directe.
  - AINS
  - CONTRASTE
- Médiée par les reins ou le contexte de néphropathie.
  - Diurétique.
  - Phosphocalcique.
- Extrarénale
  - Soit par accumulation substance.
  - Soit par changement de la fraction libre.

DALI: Le Labyrinthe

Recommandations de bonne pratique (1)

Table 4 | Drug dosing considerations for patients with CKD

Recommendations	
Clinical practice	1. A single tool to evaluate kidney function for determination of CKD and drug dosing purposes would enable delivery of high-quality care 2. It should be recognized that drug dosing recommendations developed in the era of high serum creatinine variability will be applied differently than intended in the original pharmacokinetic study 3. Clinicians should use the most appropriate tool to assess kidney function for individual patient (i.e., measured vs. estimated) 4. Metrics to determine most accurate eGFR include rigor of development process, comparison to gold standard, and measures of bias, precision, and accuracy 5. Clinical laboratories should also report eGFR in ml/min 6. Drug dosages should be adjusted according to FDA- or EMA-approved product labeling 7. When there is no information in the product label, peer-reviewed literature recommendations should be used to guide drug dosage regimen adjustments 8. Obese CKD and AKI patients and those with large variations in serum protein levels should have their drug dosage individualized based on the best available evidence
Research	1. Rigorously conducted PK/PD studies are needed to evaluate the impact of CKD on all drugs. The analysis of these studies should generate dosage regimen recommendations based on continuous relationship between GFR and clearance as well as V_D when evident 2. Categorical dosage recommendations should be based on pharmacokinetic and exposure response, not predetermined categories of kidney function 3. Evaluate the relationship between steady-state drug and metabolite exposure when appropriate on drug safety and efficacy in patients with CKD enrolled in phase II and III and/or postmarketing studies 4. Evaluate the impact of interactions of all drugs commonly used in CKD patients (e.g., phosphate binders, PPI) 5. Design and test methods to translate knowledge of PK/PD and drug interactions into clinical practice (e.g., clinical decision support systems) 6. Develop database of patients with CKD with PK/PD data and outcomes (safety/efficacy) data 7. Examine differences in dosing efficacy and safety related to the use of various kidney function indices
Regulatory	1. Drug labeling should state the strength of evidence for dosing modifications for CKD patients 2. Pharmacokinetic studies in healthy normal volunteers and CKD stage 1-5 patients should be conducted for all renally eliminated drugs 3. Reduced PK studies should be performed for all drugs. Study population should include patients on HD and the study should be initiated on a non-HD day 4. Measured GFR should be the standard for renal function and the relationship between PK/PD parameters and multiple estimating equations should be assessed 5. Pharmacokinetic data from CKD patients provided to FDA should be publicly available and accessible in user-friendly format 6. Drug labels should indicate the dosage recommendations based on measured GFR rather than a specific estimation equation 7. Further evaluations of the safety and efficacy of the proposed dosage regimens should be assessed in postmarketing studies in patient populations not sufficiently represented in premarketing studies

Drug dosing consideration in patients with acute and chronic kidney disease—a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO) Gary R Matzke et al.*Kidney International 80, 1122-1137*

Recommandations de bonne pratique (2)

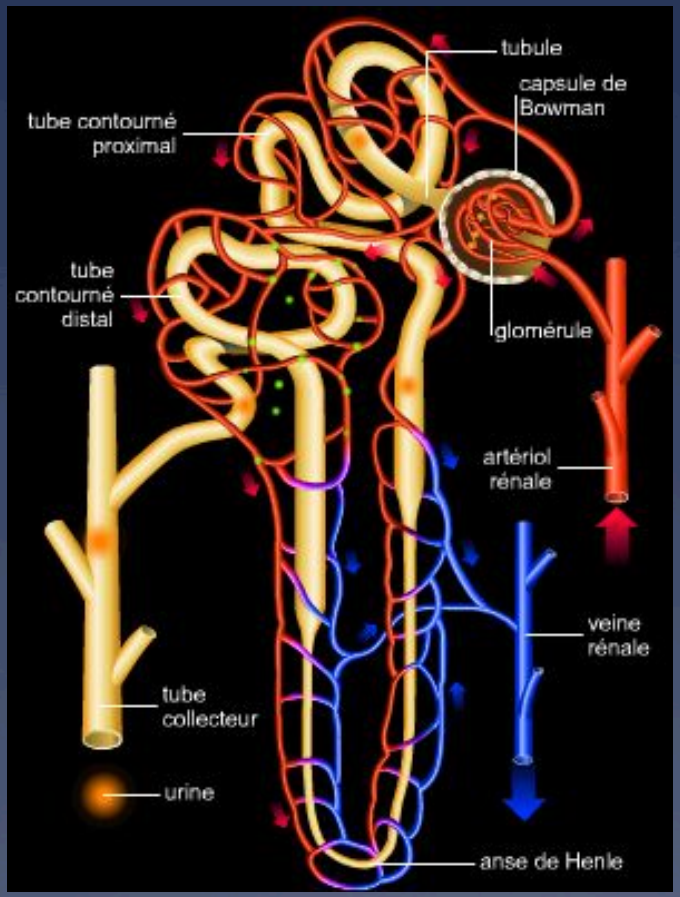
1	**Histoire du patient**	**Réaction préalable, risque de CKD**
2	Evaluation de la fonction rénale	Ajusté à la masse du patient et au Volume de distribution.
3	Identifier les médications relevantes	Ajustement primaire
4	Calculer la dose requise	Ajustement à la fonction rénale en fonction du but recherché selon FDA/EMA ou recherche de la littérature.
5	Monitoring	Dosage de la médication quand possible
6	Titration	Se baser sur la réponse clinique

QUELQUES TRUCS EST ASTUCES

- QUIZZ: 69 ans, CKD II, Cardiopathie FE 40%, Diabète II. Lisinopril 20 mg, Furosémide 40 mg 2x, Nebivolol5 mg , Aspirine 100,Moxonidine 0,4 soir, Amiodarone200, Inh sincrétine, Metformine 850 2x, D Cure /semaine,
- → RAGE DE DENT AVEC TUMEFACTION IMPORTANTE: AB /DENTISTE

IEC – ARBS – IDR – IMR

Les anti protéinuriques classiques de la néphrologie.



Protéinurie et Rein

IEC – ARBS – IDR – IMR : Comment prescrire

Les bonnes questions	Les réponses
1. Indication	Rein ? Cœur ? HTA ?
2. Fonction rénale	Tolérance à la diminution de pression glomérulaire: a.25 % de la FG b.Voir effet sur pente de créatinine
3. Ionique	Effet sur la kaliémie.
4. Association	Majoration E.S
5. Démonstration du bénéfice	Suivi clinique / paraclinique
6. Critère d'arrêt	E.S. non tolérable. Toujours en phase aigue d'une diminution de perfusion rénale ou de bloc post rénale (transitoire).

IEC – ARBS – IDR – IMR : Attente des associations

Table 4 | Summary of recommendations based on clinical evidence for the use of dual blockade of the renin–angiotensin system with ace inhibitors and angiotensin receptor blockers for cardiovascular and chronic kidney disease

Cardiovascular disease
- Hypertension
  - Level of evidence D: No clinical evidence that supports recommendation for combination therapy in hypertension
- Congestive heart failure
  - Preserved ejection fraction
    - Level of evidence D: No clinical evidence that supports recommendation for combination therapy
  - Reduced ejection fraction
    - Level of evidence B: No clinical evidence that supports recommendation for combination therapy for all-cause mortality, consideration for combination therapy to reduce hospitalization for congestive heart failure or reduce cardiovascular death
- Ischemic heart disease
  - Preserved ejection fraction
    - Level of evidence D: No clinical evidence that supports recommendation for combination therapy
  - Reduced ejection fraction
    - Level of evidence D: No clinical evidence that supports recommendation for combination therapy

Chronic kidney disease
- Diabetic kidney disease
  - Microalbuminuria
    - Level of evidence I: Limited clinical evidence that supports recommendation for combination therapy
  - Macroalbuminuria
    - Level of evidence I: Limited clinical evidence that supports recommendation for combination therapy and awaiting further clinical trial evidence for guidance
- Non-diabetic kidney disease
  - Proteinuria < 500 mg/day
    - Level of evidence I: Limited clinical evidence that supports recommendation for combination therapy and awaiting further clinical trial evidence
  - Proteinuria $\geqslant 500$ mg/day
    - Level of evidence C: Limited clinical evidence that supports recommendation for combination therapy but favors use while awaiting further clinical trial evidence

Level of evidence based on the US Preventive Services Task Force. Level A: good scientific evidence suggests that the benefits of the clinical service substantially outweigh the potential risks. Clinicians should discuss the service with eligible patients. Level B: at least fair scientific evidence suggests that the benefits of the clinical service outweigh the potential risks. Clinicians should discuss the service with eligible patients. Level C: at least fair scientific evidence suggests that there are benefits provided by the clinical service, but the balance between benefits and risks are too close for making general recommendations. Clinicians need not offer it unless there are individual considerations. Level D: at least fair scientific evidence suggests that the risks of the clinical service outweigh potential benefits. Clinicians should not routinely offer the service to asymptomatic patients. Level I: Scientific evidence is lacking, of poor quality, or conflicting, such that the risk versus benefit balance cannot be assessed. Clinicians should help patients understand the uncertainty surrounding the clinical service.

Combination inhibition of the renin–angiotensin system: is more better?

Michelle W. Krause[1], Vivian A. Fonseca[2] and Sudhir V. Shah[1]

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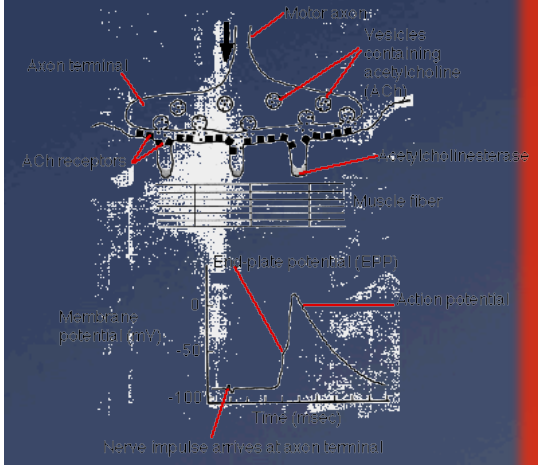
Received 1 October 2010; revised 9 February 2011; accepted 22 March 2011; published online 1 June 2011

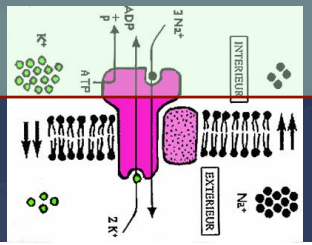
Kidney International (2011) **80**, 245–255

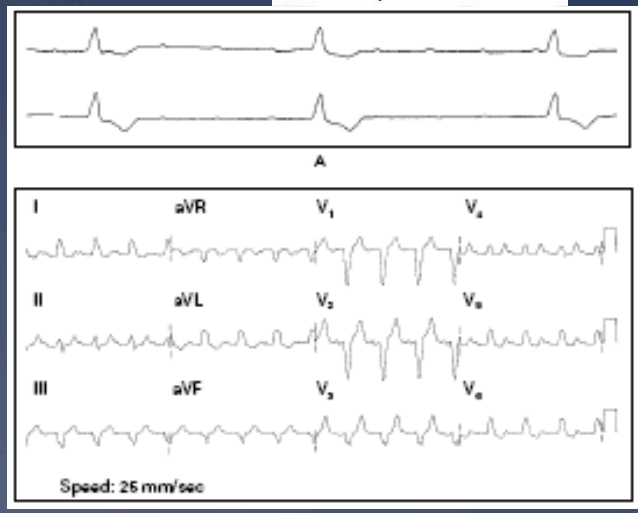
Kaliémie: hyperkaliémie



- CAUSES…
- REGIME.
  - Café – chocolat.
  - Fruit /Légume.
- Diurétique
- Chélateur
- Bicarbonate.

Intracellulaire





Chélateur du potassium

Kayexalate sodique	Kayexalate calcique	Sorbisterit calcique
Apport sodé et phosphophoré Déplétion magnésium	Acidification Apport calcique Déplétion magnésium	Apport calcique. Déplétion magnésium
DANGER DE KAYEXALOME – NECROSE COLIQUE…		

Quelle tolérance pour la kaliémie ?

ACIDOSE METABOLIQUE

Clinique:

Dyspnée.
Polypnée de repos.
Anorexie .
Patient catabolique.

Laboratoire:
Res Alcaline
CO_2

Gaz sanguin.

Facteur de risque de progression rénal!

Traitement
Diurétique alcalinisant
Eau Alcalinisée (titration par verre)
Magistrale de bicarbonate de sodium ou d'acetate de sodium (Phoslo)

Diurétiques

- Principe: les diurétiques ne sont pas toxiques dans leur bonne indication…
- **Indication :**
  - **Hypervolémie à corriger .**
  - **HTA (! Sans déshydrater le patient !).**
- Toxicité:
  - Déshydratation (surdosage).
  - Trouble ionique
  - Déséquilibre acido basique (rarement investigué!)
  - Majoration toxicité en association.
  - divers

Diurétiques

	De l'Anse	thiazidique	Épargne potassique	Diamox	Vaptan
K	↓	↓	↑		
Na	↓	↓	↓	↓	
CL	↓	↓	↓	↓	
CO2	↑	↑	↓	↓	
Ca	↓	↑			
Mg	↓	↓			
H2O	↓				↓

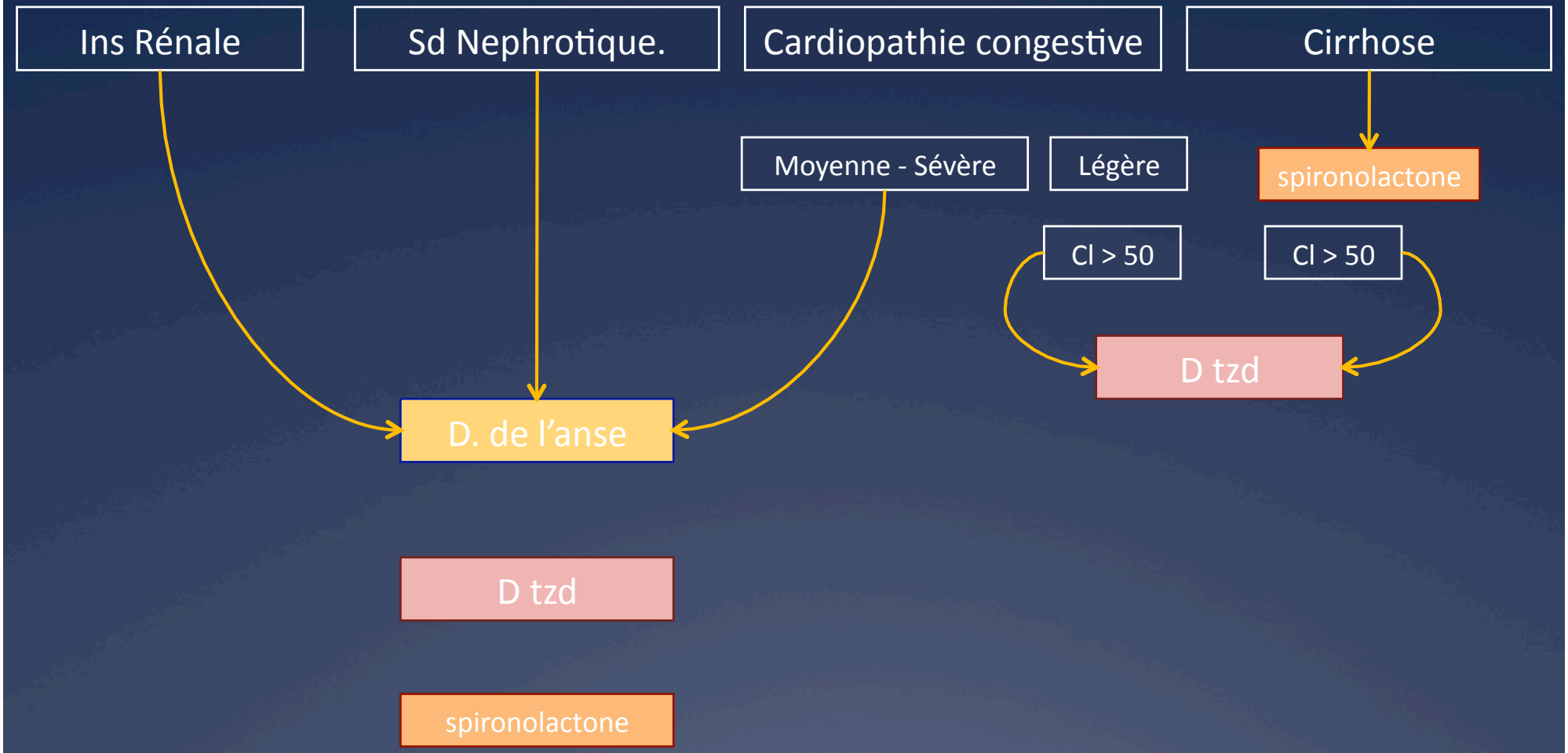
394.Martinez-Maldonado, M. and H. R. Cordova. Cellular and molecular aspects of the renal effects of diuretic agents. Kidney Int. 38: 632–641, 1990.

http://www.cybermedicine2000.com/pharmacology2000/Autonomics/Adrenergics1/Adrenergic-46.htm

Résistance aux diurétiques

- Adhérence du patient ?
  - Prise de NaCL / H2O
  - Oubli du traitement
  - Effet « rebond »
- Absorption ?
- Physiopathologie ? (ex cirrhose)
- Hypoalbuminémie.
- Volume sanguin circulant.
- AINS.

Ligne de conduite

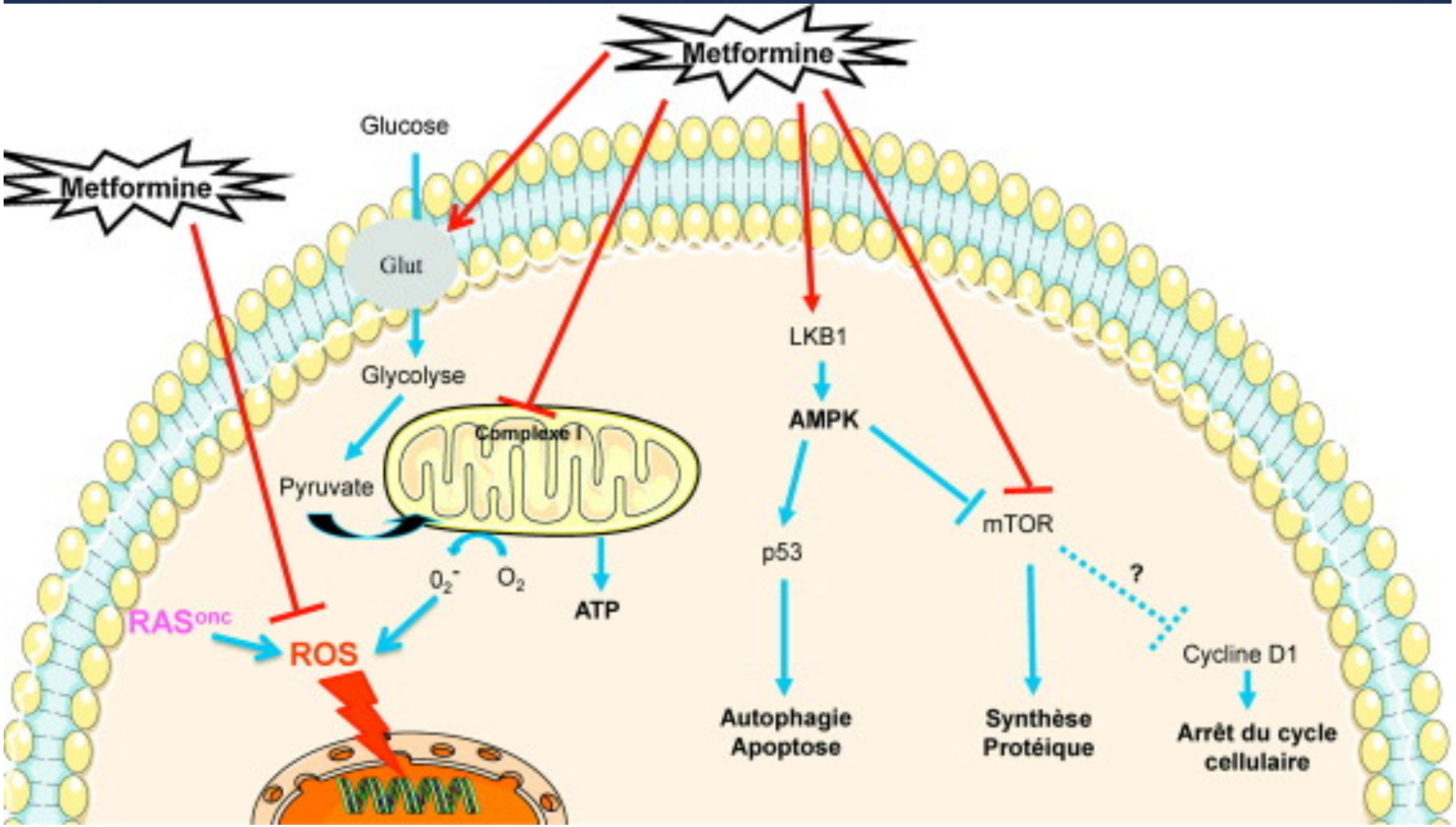


Drug Therapy, Review Article Diuretic therapy D.Craig Brater, MD, NEJM 1998

Metformine et lactate - story

- Insulino-sensibilisant, dérivé de la guanidine
- Première ligne pour le traitement du diabète de type II.
- = Biguanide
  - Inhibition néoglucogenèse et glycogénolyse hépatique (et rénale)
  - Favorise captation du glucose par le muscle + glycolyse
  - Réduction lipogenèse
  - Inhibition captation intestinale de glucose
  - Inhibition spécifique du complexe I de la CRM
- Mécanisme : activation AMPK

Metformine : mécanismes d'action



Metformine et lactate mécanisme

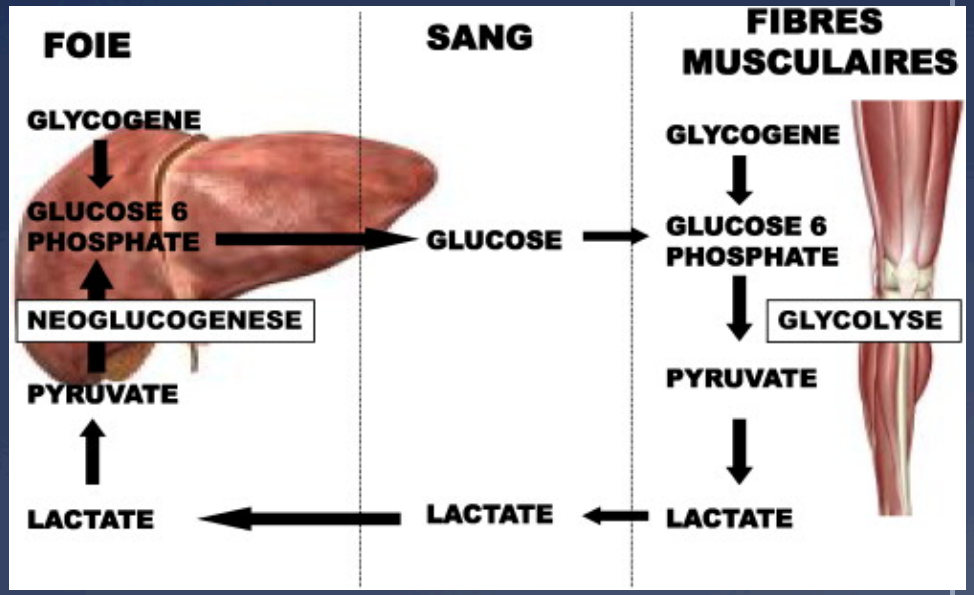
- Pas d'autre cause à l'hyperlactatémie
- Inhibition néoglucogenèse → Augmentation du taux de lactate dans le sang
- Augmentation du taux de Metformine dans le sang
  - IR/IH/IC
  - Overdose (TS, erreur)
- Fonction mitochondriale des hépatocytes compromise
  - Augmentation du lactate = épiphénomène du à l'inhibition.

Metformine et lactate: patient à risque

- !!Prescription diurétique, AINS, IEC ou association
- CI à la prescription de Metformine :
  - IR avec clearance créatinine < 40ml/min ou créatinine plasmatique > 1,5mg/dL
  - IH
  - IC
  - Athérosclérose sévère
  - **Alcoolisme**
- Arrêt Metformine si :
  - GASTRO ENTERITE
  - AG
  - Intervention chirurgicale ou toute intervention pouvant provoquer une IR a *posteriori* (contraste,…).
  - IMC, infection sévère, grossesse ou allaitement, choc.

Clearance du lactate

* Hépatique : Cycle des CORI

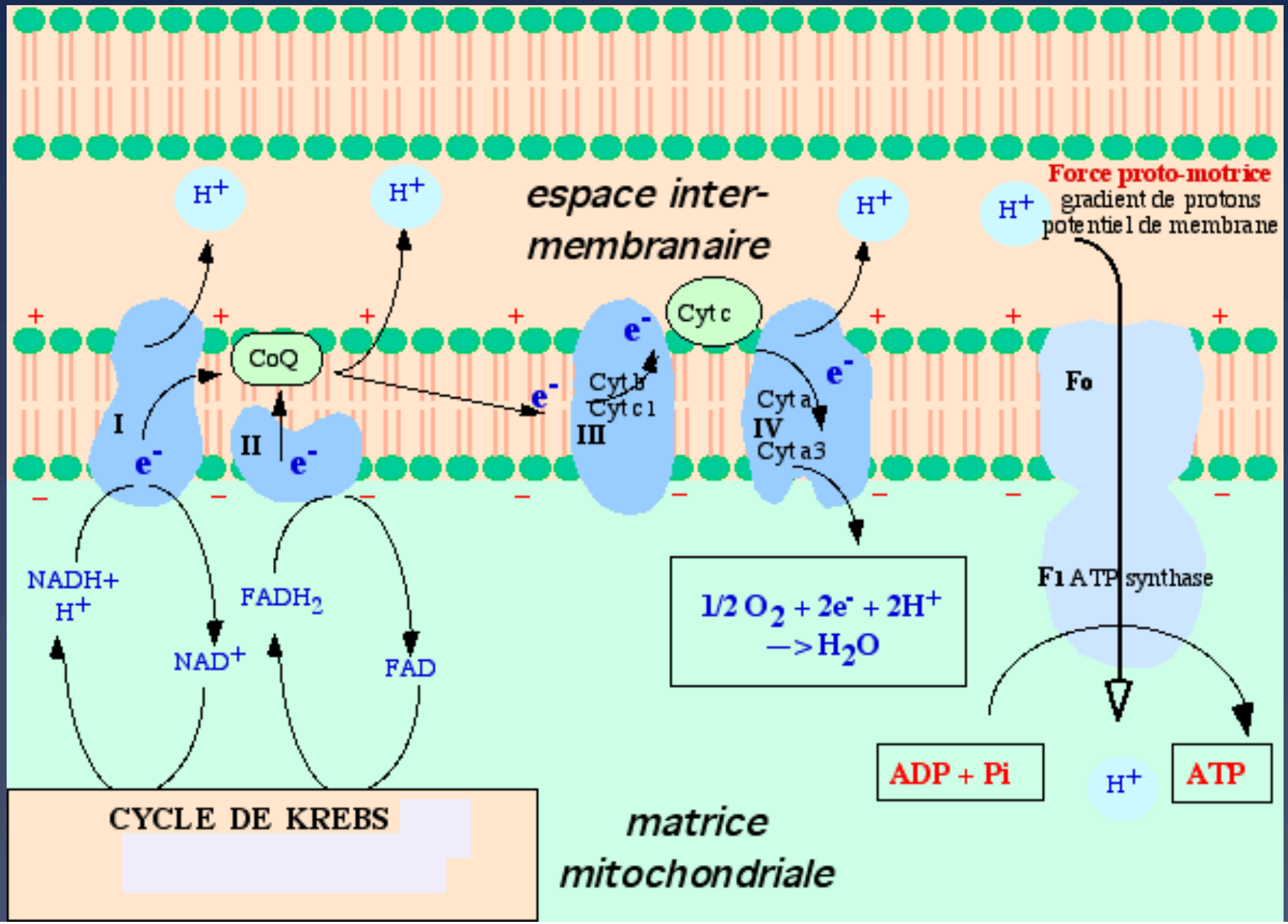


70% (3400 mmol/24h)

* Corticale rénale
  * Néoglucogenèse rénale du lactate extracellulaire
  * Augmentation de l'élimination urinaire de lactate (si pas d'IR).
  * Aucune explication dans les livres de physiologie…

<30%

Chaine respiratoire mitochondriale



METFORMINE en pratique

MEDECIN

* ADAPTER CLEARANCE
* < 60 Diminuer
* < 30 Exception qui doit être médicalement expliquée
* SURVEILLANCE EDUCATION

NON MEDECIN

* CAHIER DE SOINS.
* EDUCATION PATIENT
* EDUCATION ENTOURAGE

SI PHASE AIGUE / DESHYDRATATION / HYPOPERFUSION ARRET IMMEDIAT DE LA METFORMINE (1A)

INSULINE

- Temps de demi vie prolongé dans l'IR sévère
  - Diminution dose dans la progression
  - Risque plus important d'hypoglycémie
- Pharmacocinétique cutanée modifiée:
  - Rareté capillaire
  - Œdème.
- Trouble ionique et résistance: acidose, …

Produit de contraste iodé et rein

	commentaire
Pubmed	16339 article et 2003 review
Physiopathologie	« Nécrose tubulaire »
Prévention	Expension volumique, Alcalinisation Arrêt Diurétique Arrêt inhibiteur de l'axe (?) Lysomucil (☹)
CKD 4 & Haut risque	Hospitalisation pour protocole d'hydratation ?
Traitement	Néant !
M.G.	Contrôle de la fonction rénale au moins 15-21 jour post.

Produit de contraste iodé

Tableau I Score prédictif d'IRA post-PCI *	
Facteur de risque	Score
Age > 75	4
Diabète	3
PA systolique < 80 mmHg durant > 1h et requérant support inotrope ou ballon intra-aortique	5
Hypoperfusion rénale sévère (1)	5
DFG (2) 40 - 60 20 - 39 < 20 ml/min	2 4 6
Volume de PCI	1/100 ml

Total du score	Risque d'IRA (3) (%)	Risque de dialyse (%)
2 - 5	7.5	0.04
6 - 10	14	0.12
11 - 15	26	1.09
≥ 16	57	12.6

(1) cf texte
(2) Débit de filtration glomérulaire, calculé par la méthode de Cockcroft ou par la formule MDRD
(3) Majoration du taux de créatinine > 0.5 mg/dl ou > 25 %
* Adapté de Mehran (4)

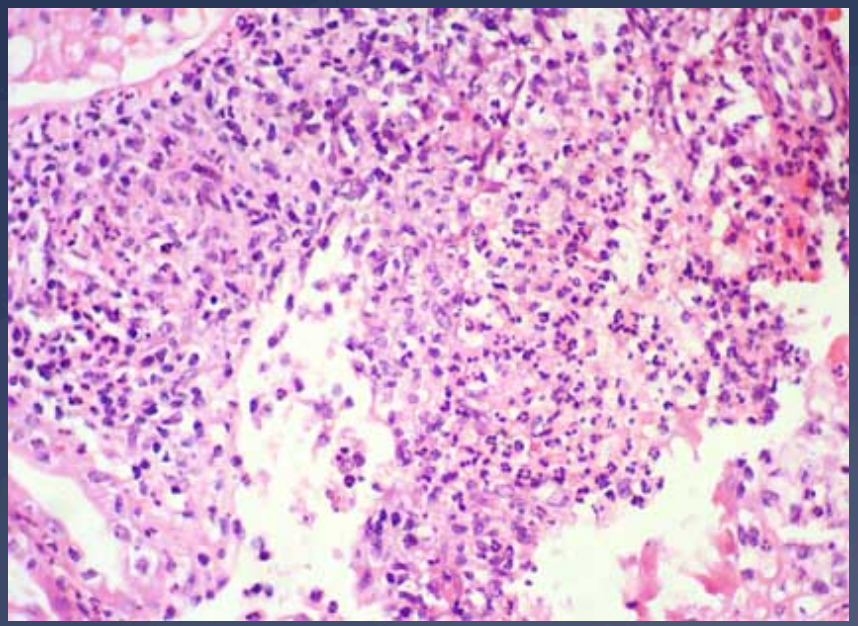
http://sites-final.uclouvain.be/loumed/V126,%202007/mai/142-147.pdf

Si le DFG est < 40 ml/min

- interrompre diurétique, AINS (et metformine ?) 48h avant l'examen

en l'absence de contre-indication, perfuser du sérum physiologique, 1 ml/kg/h, durant 24h (de 12h avant à 12h après l'examen)

Toxicité rénale: la NTIA



- Premier coupable:
  - IPP
  - AINS
  - Antibiotique
- Traitement:
  - Arrêt de la drogue incriminée.
  - Corticoïde ?
    - Améliore vitesse de recouvrement.
    - Dose et durée : aucune étude comparative.
    - Rapidité du diagnostic !
- Diagnostic P.B.R.: pourquoi ?

NTIA: Quand y penser ?

* Nouveau Traitement
* Symptôme d'AEG / néphrologique et Tigelle positive.

Nephrol Dial Transplant (2006) 21: 1994–1995
doi:10.1093/ndt/gfl045
Advance Access publication 28 February 2006

Case Report

Rosiglitazone as a cause of acute interstitial nephritis

Clare Castledine, David Wright and Edward Kingdon

Les classiques ….

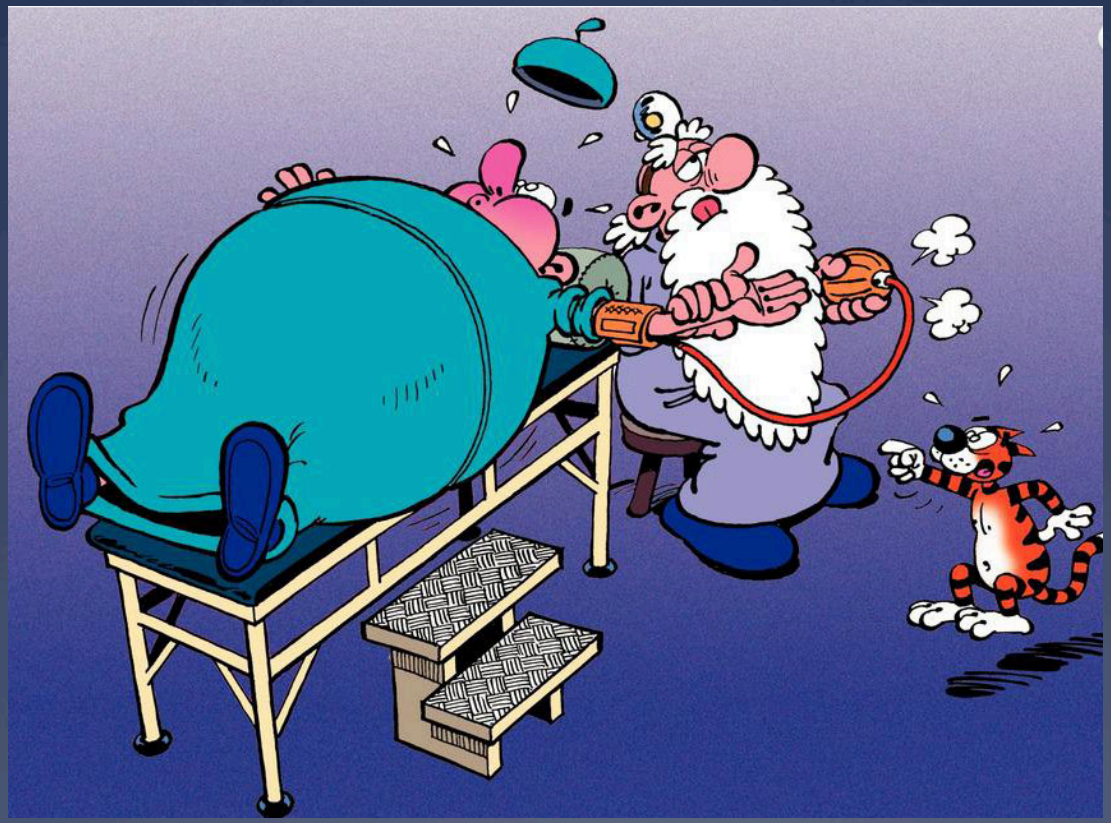
Médication	Mécanisme
Produit de contraste iodé	Toxicité tubulaire. - dose dépendant - lésion rénale préexistante.
A.I.N.S	Vasoconstriction artériolaire.: dimininution débit glomérulaire et majoration risque cardiovasculaire.
Lithium	Néphropathie interstitielle – diabète insipide.
Fleet phosphosoda	Précipité phosphaté intra tubulaire
Inhibiteur TK	Lésion glomérulaire.

QUIZZ

- Femme de 74 ans,
- Diabète , CKD IV, RTNP diabt sévère , HTA, Tumorectomie sein.
- R/ IEC FUROSEMIDE FER INSULINE BB ANTI ca AAS Calcium 1g, D Cure
- Créatinine : 3,4 mg/dL
- RECIDIVE OSSEUSE: START DENOSUMB DOSE ONGOLOGIQUE

QUIZZ

* Docteur, je me sens épuisée, , j'ai des picotements dans les mains … des crampes...et des palpitations.



REMERCIEMENTS

R.U.M.B
Mme Sigrid Lebeau
Médecins MB

www.nephrologue.be