

Evaluer la fonction rénale

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Liens d'intérêt

- Research grants: MSD, Astute medical
- Speaker fees: MSD, Astellas, Bristol Myers Squibb, Gilead
- Support in organizing educational meetings: MSD, Astellas, JazzPharma
- Advisory board: Sanofi Aventis, Gilead-Kite

Plan de la présentation

- Définition de l'insuffisance rénale et notion de réserve fonctionnelle
- Marqueurs usuels
- Ce qui n'est pas encore validé
- Ce qui est à venir
- Conclusion

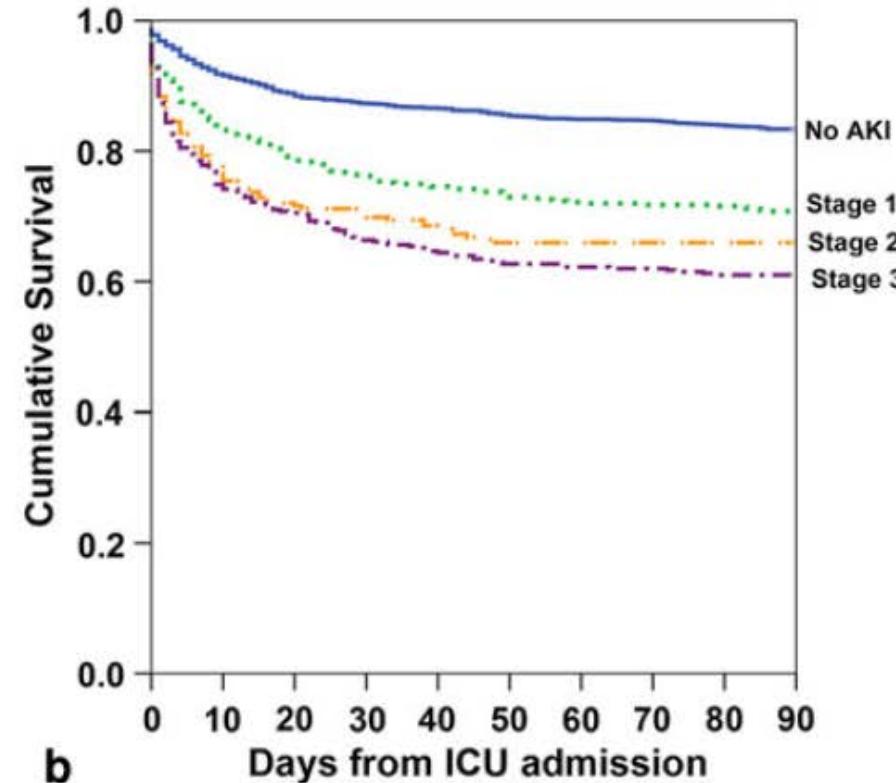
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Définition de l'insuffisance rénale

Stage	Serum Creatinine	Urine Output
1	↑ Creatinine > 26.4 $\mu\text{mol/L}$ or creatinine x 1.5-1.99	< 0.5 $\text{ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ for 6-12h
2	Creatinine x 2-2.99	< 0.5 $\text{ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ for 12h+
3	↑ Creatinine > 355 $\mu\text{mol/L}$ or creatinine x 3+ or initiation of RRT	< 0.3 $\text{ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ for 24h or anuria for 12h+

Insuffisance rénale aigue et devenir



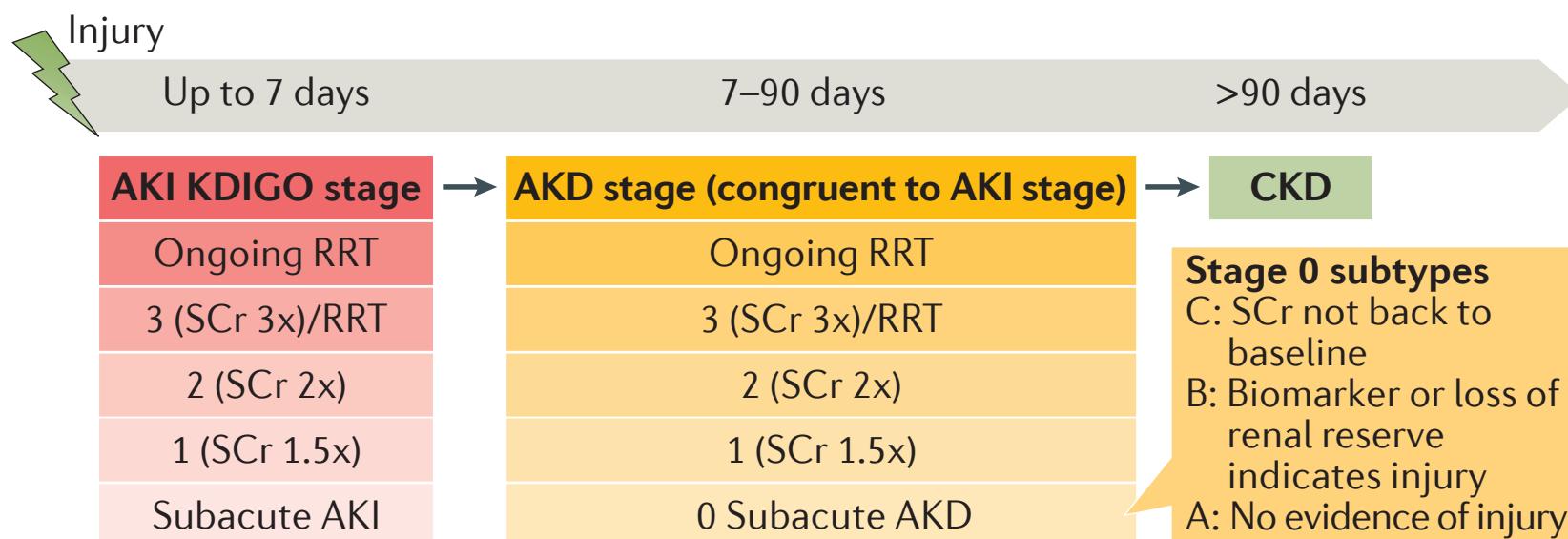
Un processus évolutif

Durée de l'IRA:

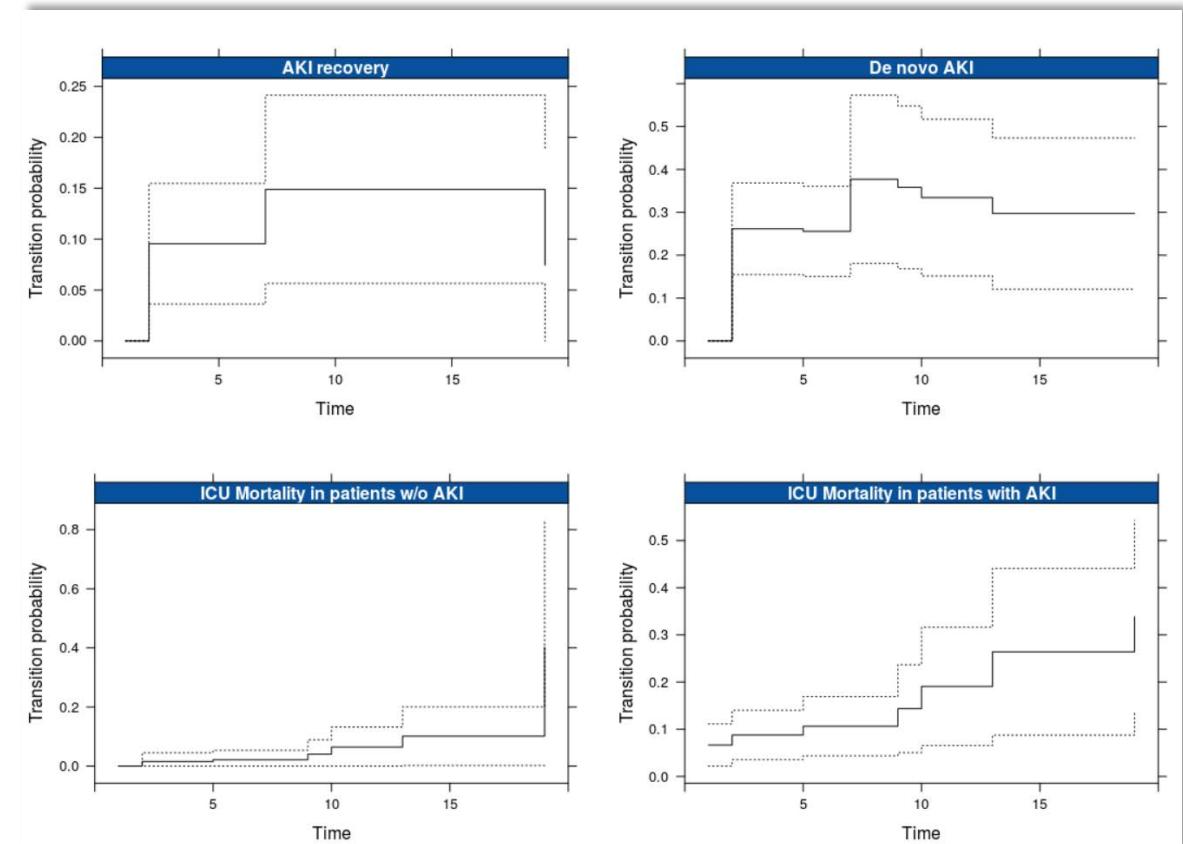
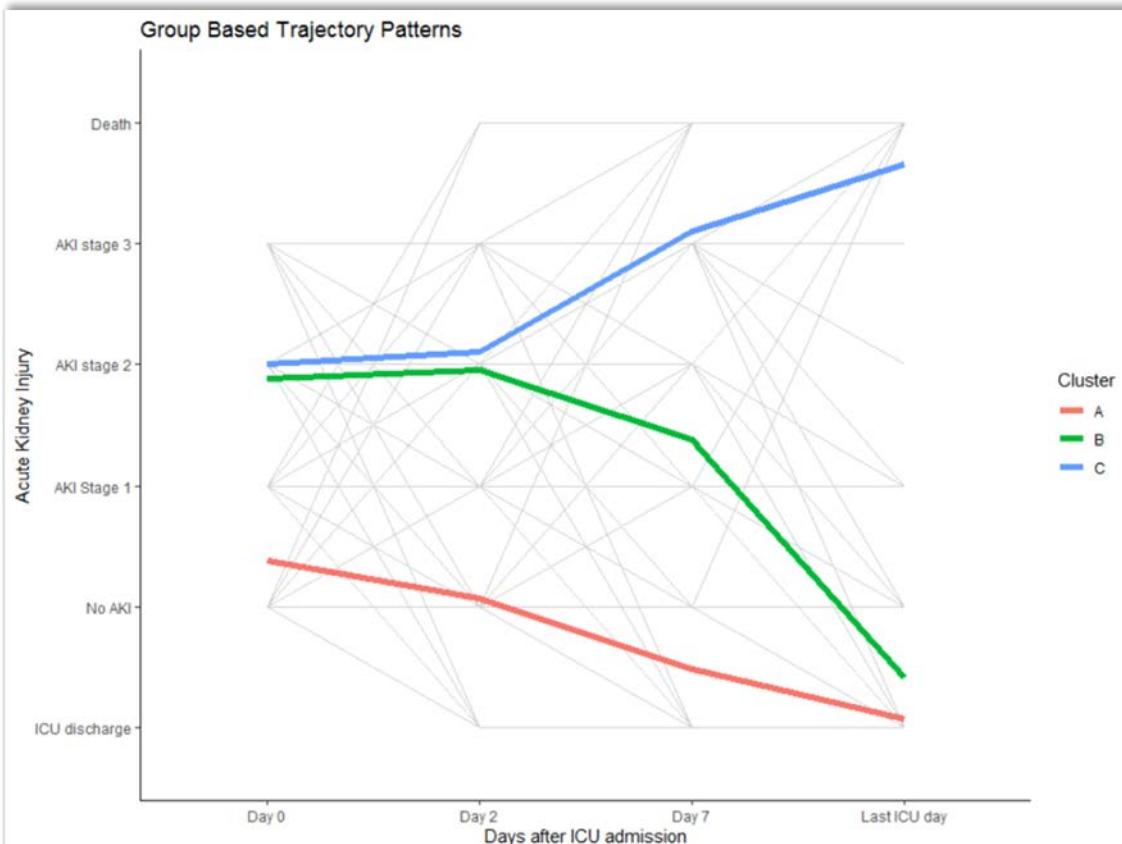
0-2 Jours : IRA Rapidement réversible

2-7 jours: IRA persistante

7-90 jours: « Maladie rénale aiguë »



Un processus évolutif



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Créatinine plasmatique et sa cinétique

En dehors de toute maladie rénale chronique une baisse de 30 à 40% du DFG ne se traduit pas par une élévation de la créatinine

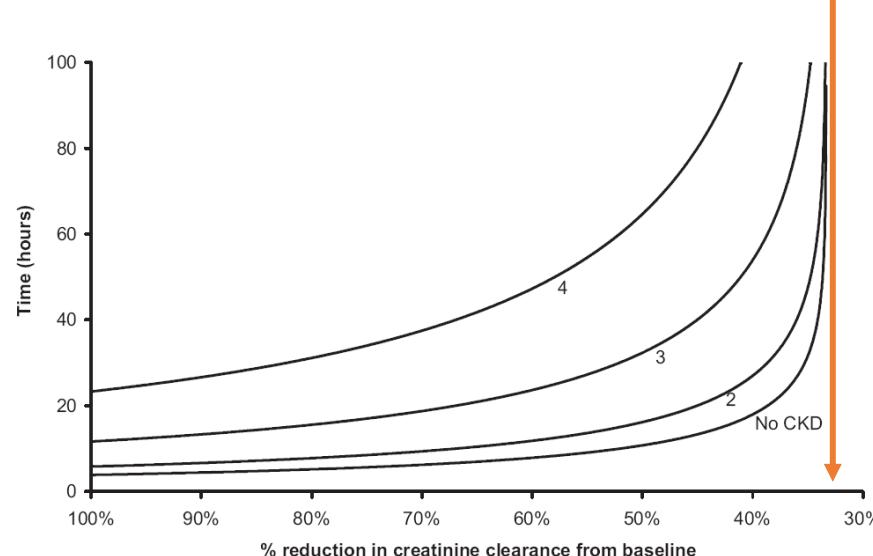


Figure 5. Time to reach a 50% increase in SCr after a given percentage reduction in CrCl, according to the absence or presence of stages 2 through 4 CKD.

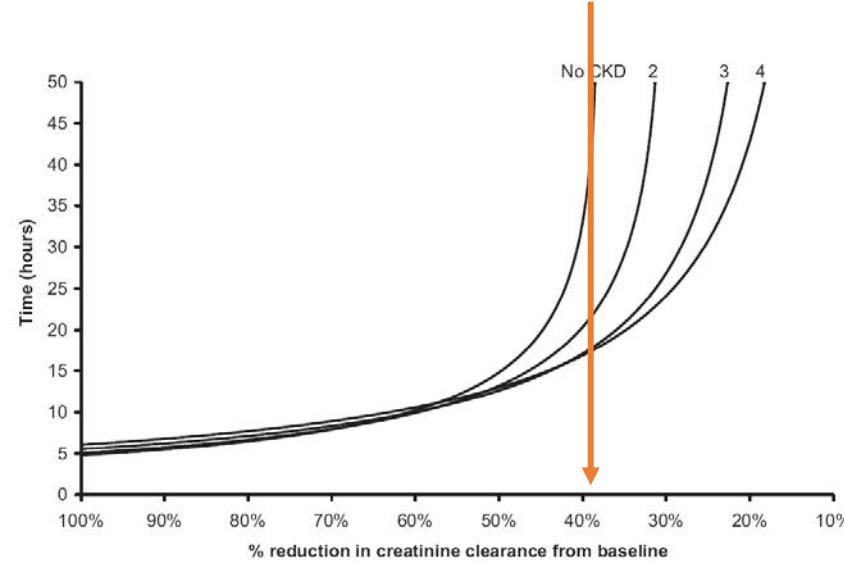


Figure 6. Time to reach a 0.5-mg/dl increase in SCr after a given percentage reduction in CrCl, according to the absence or presence of stages 2 through 4 CKD.

Créatinine plasmatique et sa cinétique

Une élévation de la créatinine dans les taux attendus par la définition de l'IRA nécessite 5 à 24h de baisse profonde du DFG

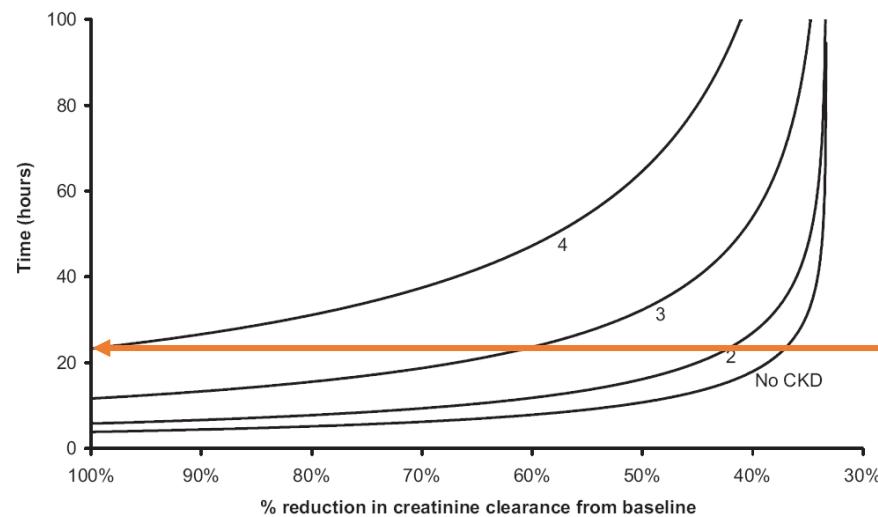


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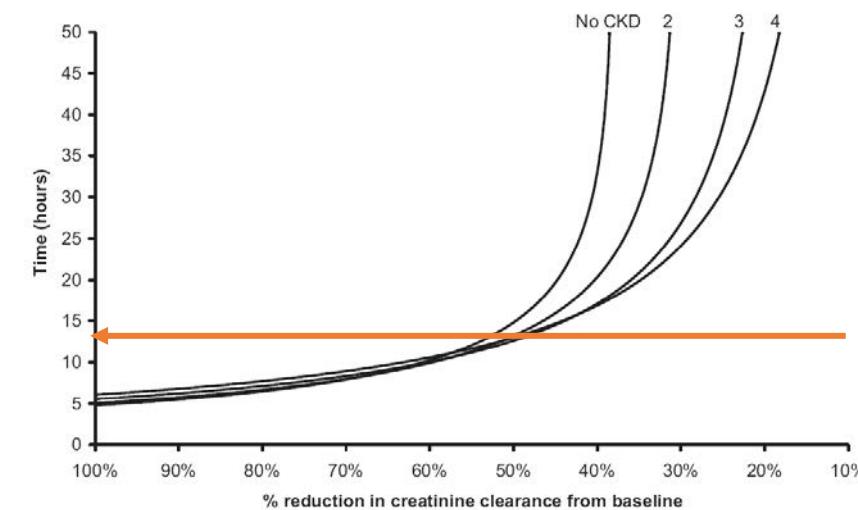
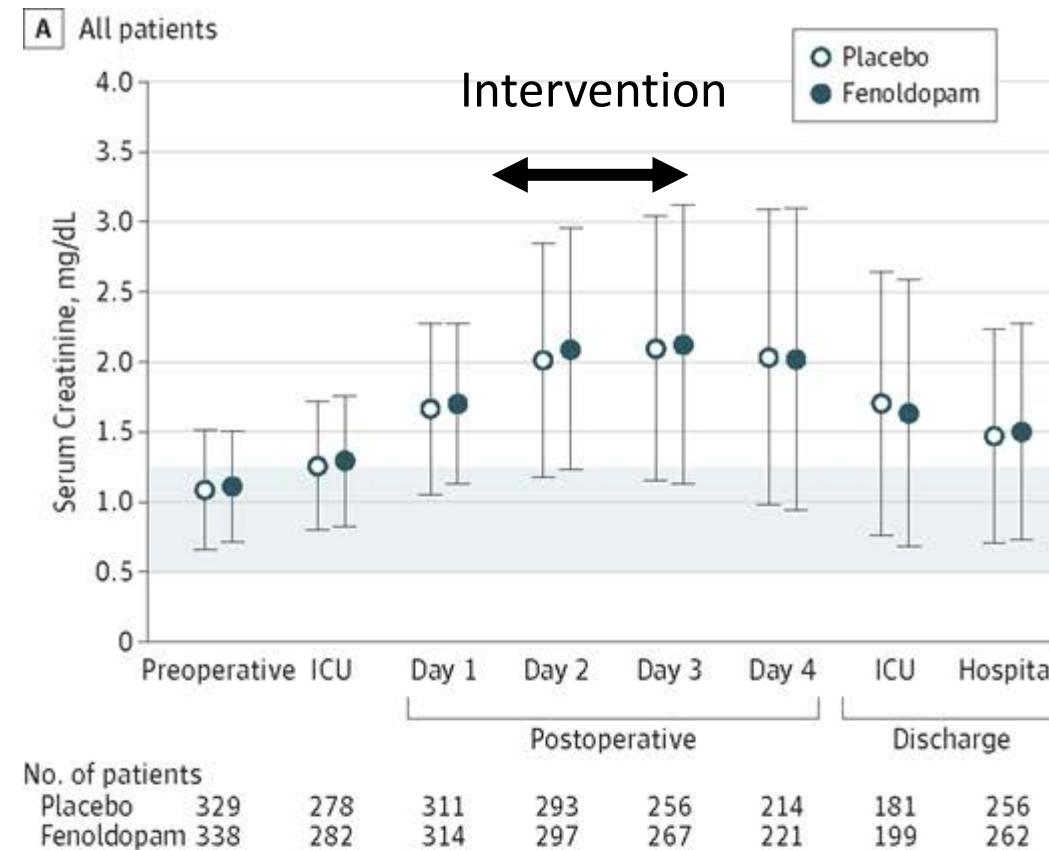


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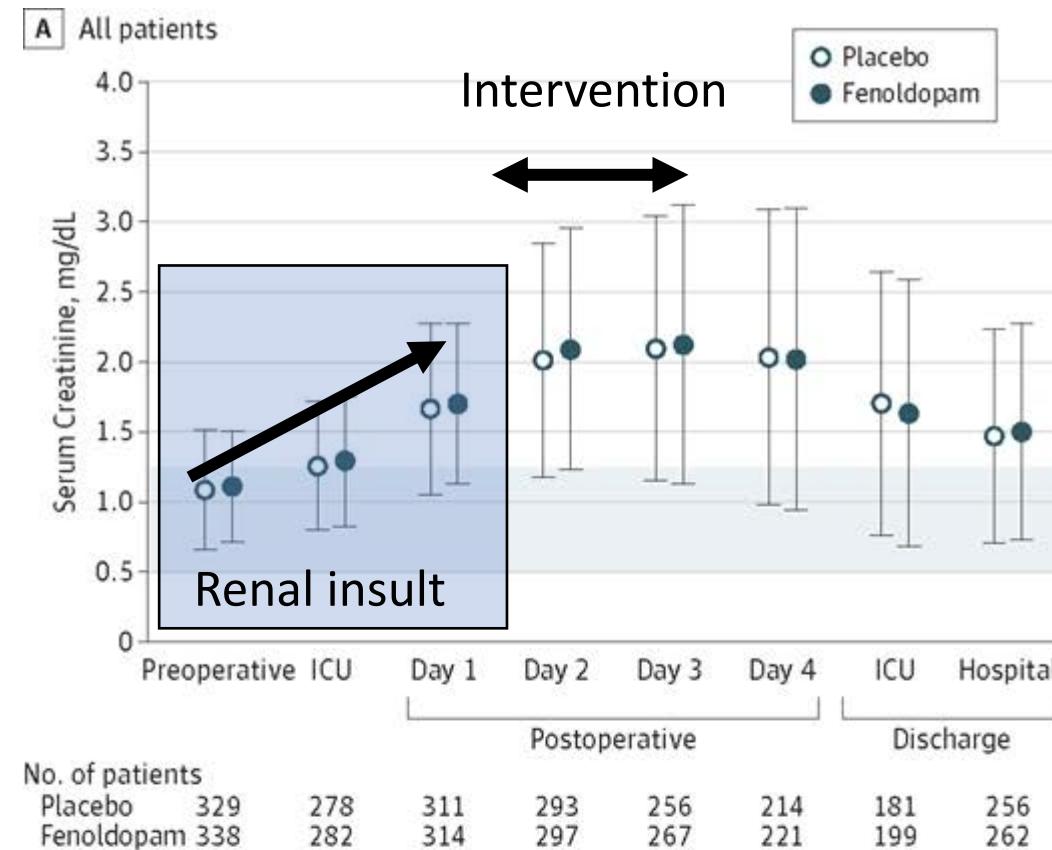
Conséquences pratiques

RCT – 129 Patients – Fenoldopam or Placebo following cardiac surgery
Randomization of patients if AKI stage RIFLE R after surgery [Median 32h (IQR 26-52)]



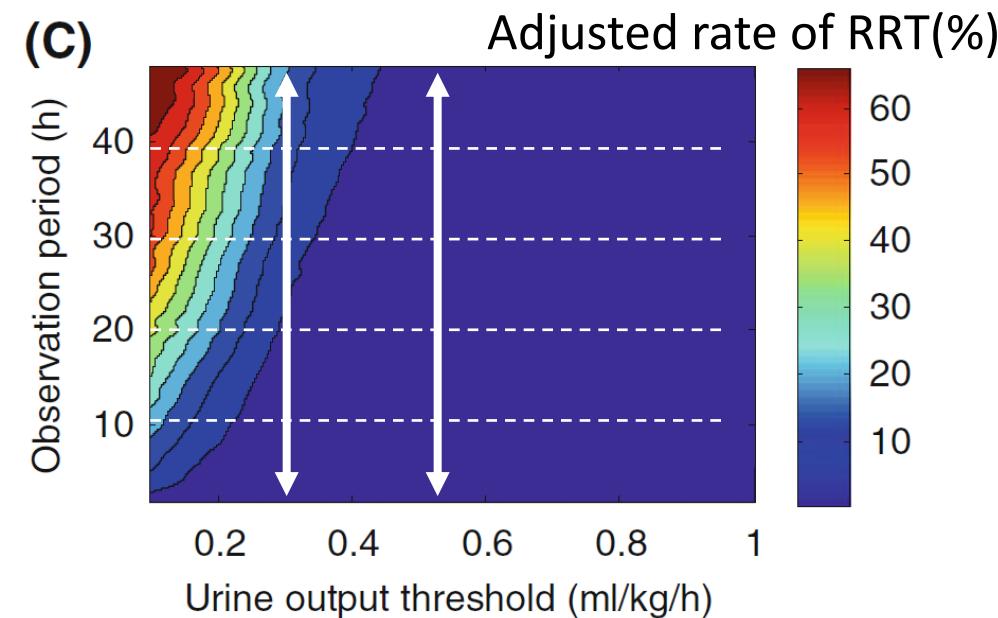
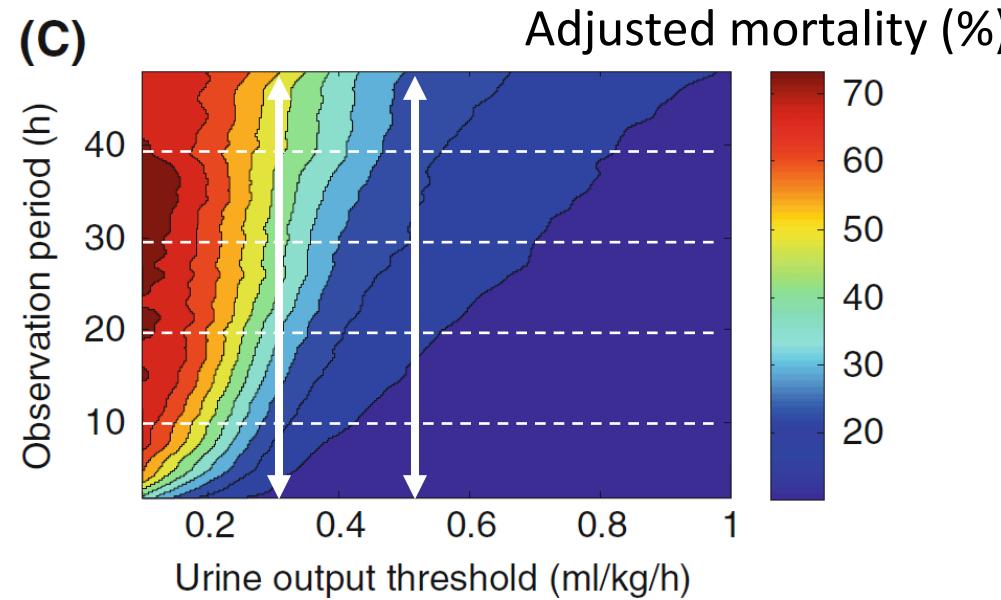
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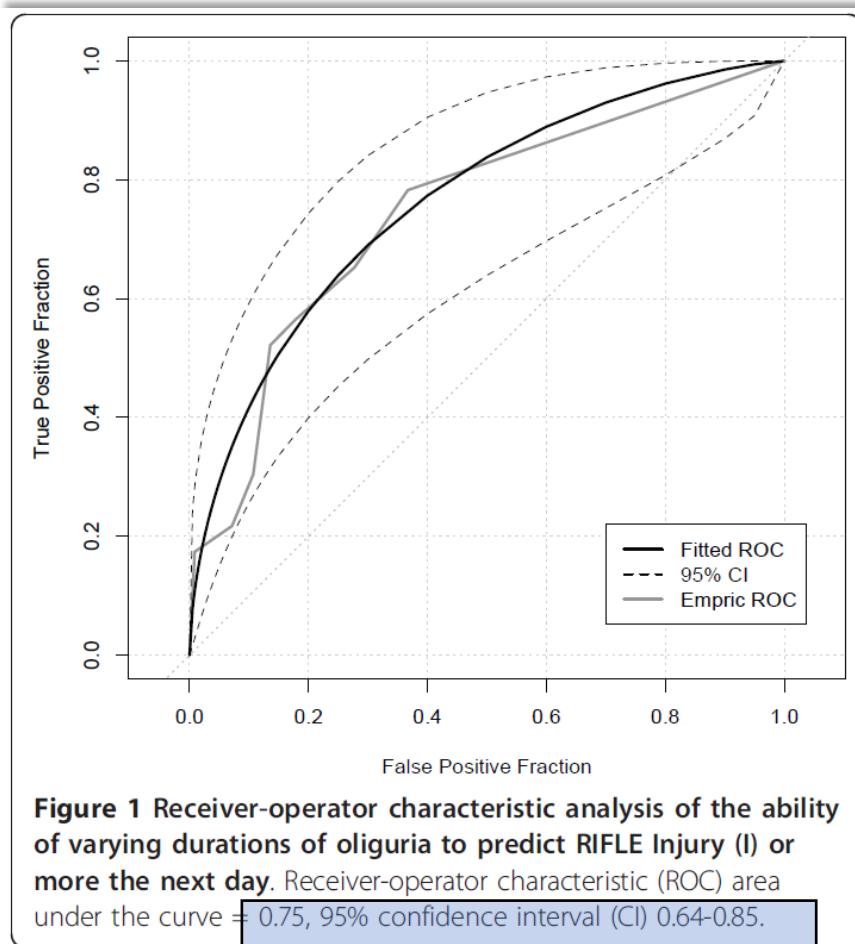


Oligurie: un marqueur peu spécifique

14,526 critically-ill patients with urine output measurement
Relationship between urine output, duration of an oliguria and outcome



Oligurie: un marqueur peu spécifique



239 ICU patients

Oliguria vs. AKI according to Screat.

Incidence of AKI-Screat: 13.4%

6 hours of oliguria :

Sensitivity : 21%

Specificity : 93%

Positive predictive value : 9%

Negative predictive value : 97%

En pratique

- Oliguria



- Creatinine change

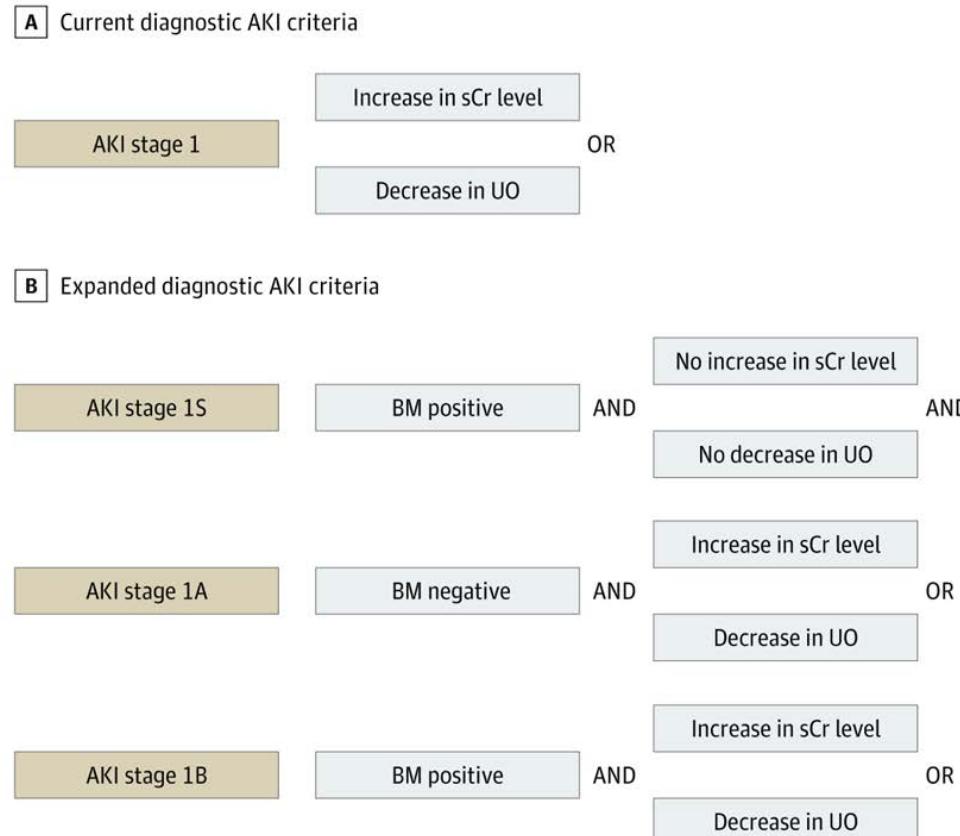


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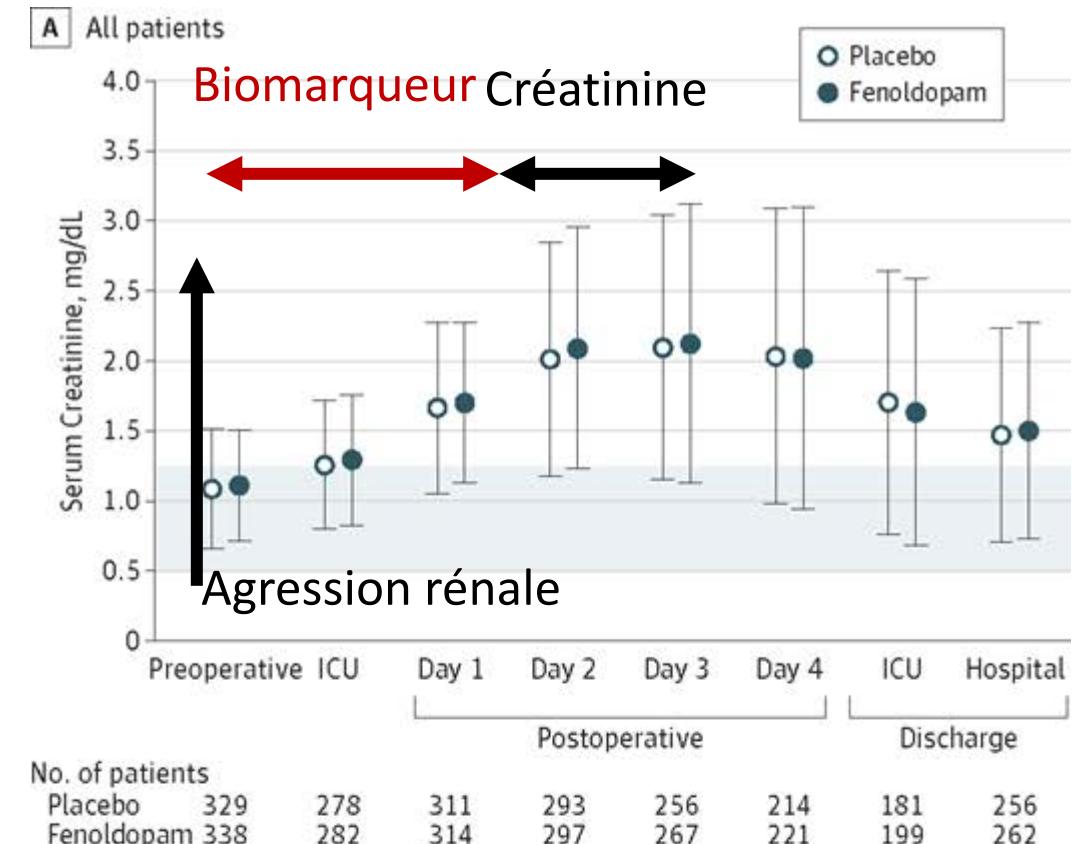
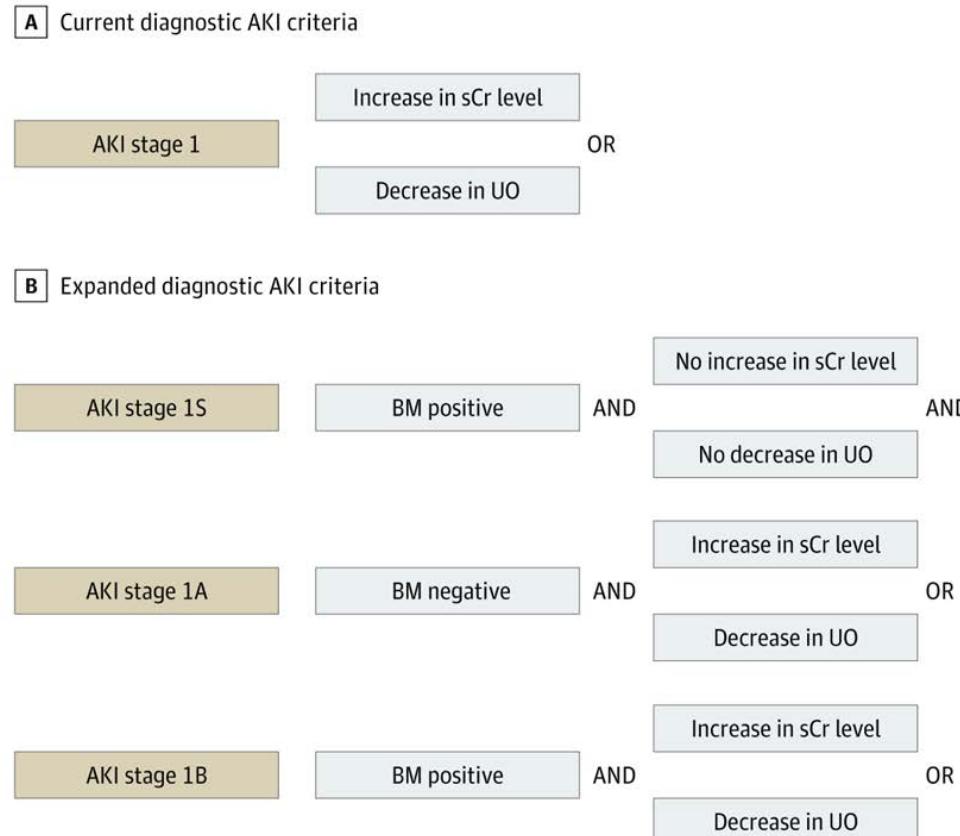
Quelle place pour les biomarqueurs?

Figure 1. Refined Staging System for the Diagnosis of Acute Kidney Injury (AKI)



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Figure 1. Refined Staging System for the Diagnosis of Acute Kidney Injury (AKI)



4 problèmes pratiques

Table. Description and Characteristics of Common Biomarkers of AKI

AKI biomarker	Biological role	Source	Stress marker ^a	Damage marker ^b	Potential role in clinical practice				
					Functional marker ^c	Risk assessment	Prediction of AKI	Diagnosis of AKI	Severity of AKI
Alanine aminopeptidase; alkaline phosphatase; γ -glutamyl transpeptidase	Enzymes located on the brush border villi of the proximal tubular cells; released into urine after tubular damage	Coca et al., ² 2008	Urine				X	X	
Calprotectin	Cytosolic calcium-binding complex; derived from neutrophils and monocytes; detectable in urine in intrinsic AKI	Charlton et al., ³ 2014; Heller et al., ⁴ 2011	Urine				X		
C-C motif chemokine ligand 14	Pro-inflammatory chemokine; released into urine following stress or damage of tubular cells	Hoste et al., ⁵ 2020	Urine						X
Chitinase 3-like protein 1	39 kDa intracellular protein of glycoside hydrolase family; expressed by endothelial cells, macrophages, and neutrophils	De Loor et al., ⁶ 2016	Urine and plasma				X		
Cystatin C	13 kDa cysteine protease inhibitor produced by nucleated human cells; freely filtered	Coca et al., ² 2008; Ho et al., ⁷ 2015; Ravn et al., ⁸ 2019	Plasma			X	X		
Dickkopf-3	38 kDa stress-induced, kidney tubular epithelia-derived glycoprotein; secreted into urine under tubular stress conditions	Schunk et al., ⁹ 2019	Urine		X	X			
α glutathione S-transferase	Cyttoplasmic enzyme in proximal tubule	Koym et al., ¹⁰ 2010	Urine				X		
η glutathione S-transferase	Cyttoplasmic enzyme in distal tubules	Coca et al., ² 2008; Charlton et al., ³ 2014	Urine				X		
Hepatocyte growth factor	Antifibrotic cytokine produced by mesenchymal cells and involved in tubular cell regeneration after AKI	Heller et al., ⁴ 2011; Vaidya et al., ¹¹ 2008	Plasma				X	X	
Hepcidin	2.78 kDa peptide hormone predominantly produced in hepatocytes; freely filtered	Ho et al., ⁷ 2015	Urine and plasma			X	X		
Tissue metalloproteinase-2; insulin-like growth factor binding protein-7	Metalloproteinases released during cell cycle arrest	Kashani et al., ¹² 2013; Ostermann et al., ¹³ 2018; Joannidis et al., ¹⁴ 2019	Urine			X	X	X	
Interleukin-18	18 kDa pro-inflammatory cytokine; released into urine following tubular damage	Coca et al., ² 2008; Ho et al., ⁷ 2015	Urine			X	X		
Kidney injury molecule-1	Transmembrane glycoprotein produced by proximal tubular cell; released into urine after tubular damage	Coca et al., ² 2008; Ho et al., ⁷ 2015; Koym et al., ¹⁰ 2010	Urine			X	X	X	
Liver-type fatty acid-binding protein	14 kDa intracellular lipid chaperone; freely filtered and reabsorbed in proximal tubule; urinary excretion after tubular cell damage	Ho et al., ⁷ 2015	Urine and plasma				X		
MicroRNA	Endogenous single-stranded non-coding nucleotides; >50 individual microRNAs are expressed in AKI, especially in association with inflammation, apoptosis and fibrosis	Fan et al., ¹⁵ 2019	Urine and plasma				X		
Monocyte chemoattractant peptide-1	Peptide expressed in tubular epithelial cells, kidney mesangial cells and podocytes; released into urine	Moledina et al., ¹⁶ 2017	Urine				X		
N-acetyl- β -D-glucosaminidase	>130 kDa lysosomal enzyme; released into urine after tubular damage	Charlton et al., ³ 2014	Urine				X		
Neutrophil gelatinase-associated lipocalin	At least 3 different types: (1) monomeric 25 kDa glycoprotein present in neutrophils and epithelial tissues, including tubular cells; (2) homodimeric 45 kDa protein produced by neutrophils; (3) heterodimeric 135 kDa protein produced by tubular cells	Coca et al., ² 2008; Ho et al., ⁷ 2015; Charlton et al., ³ 2014	Urine and plasma			X	X		
Netrin-1	50–75 kDa laminin-related molecule minimally expressed in proximal tubular cells of normal kidneys; released into urine after tubular cell damage	Ramesh et al., ¹⁷ 2010	Urine				X		
Osteopontin	Glycoprotein expressed in tubular cells and interstitial infiltrating cells in areas of tubulointerstitial damage	Lorenzen et al., ¹⁸ 2011	Plasma			X	X		
Proenkephalin A	Endogenous polypeptide hormone in adrenal medulla, nervous system, immune system and renal tissue; freely filtered	Legrand et al., ¹⁹ 2019	Plasma			X	X	X	
Retinol binding protein	21 kDa glycoprotein; synthesized by liver; filtered by glomeruli and reabsorbed by proximal tubules; released into urine following tubular damage	Charlton et al., ³ 2014	Plasma						
Tumor necrosis factor	Pro-inflammatory cytokine; released after tubular damage	Ho et al., ⁷ 2015	Plasma			X			

Abbreviation: AKI, acute kidney injury.

^a Stress markers indicate cell stress; cell stress can resolve or progress to damage or alter kidney function.

^b Damage markers indicate structural damage that may or may not be associated with reduced kidney function. These molecules include constitutive proteins released by the damaged kidney, molecules upregulated in response to injury, or nonkidney tissue products that are filtered, reabsorbed, or secreted by the kidney.

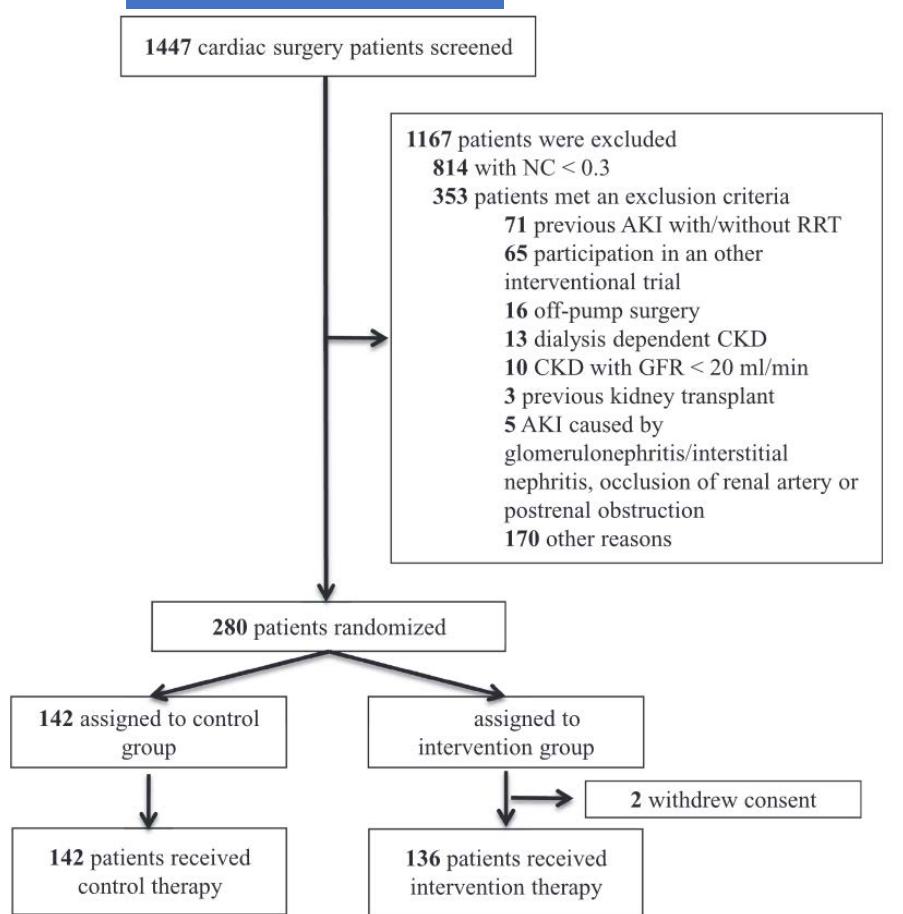
Non recommandé en pratique à ce jour car

- 1- Aucun marqueur n'a démontré une performance satisfaisante
- 2- Aucun marqueur n'a démontré un bénéfice à son utilisation
- 3- La confusion entre marqueur fonctionnel et marqueur lésionnel a grandement limité l'interprétation des données
- 4- Le marqueur idéal va induire une modification de prise en charge

Une attention accrue est portée à ce jour sur le TIMP2*IGFBP7 (marqueur d'agression) et CCL14 (marqueur pronostic)

Etudes PrevAKI (?)

Inclusion si NC >0.3



Traitement standard

Bundle de prévention

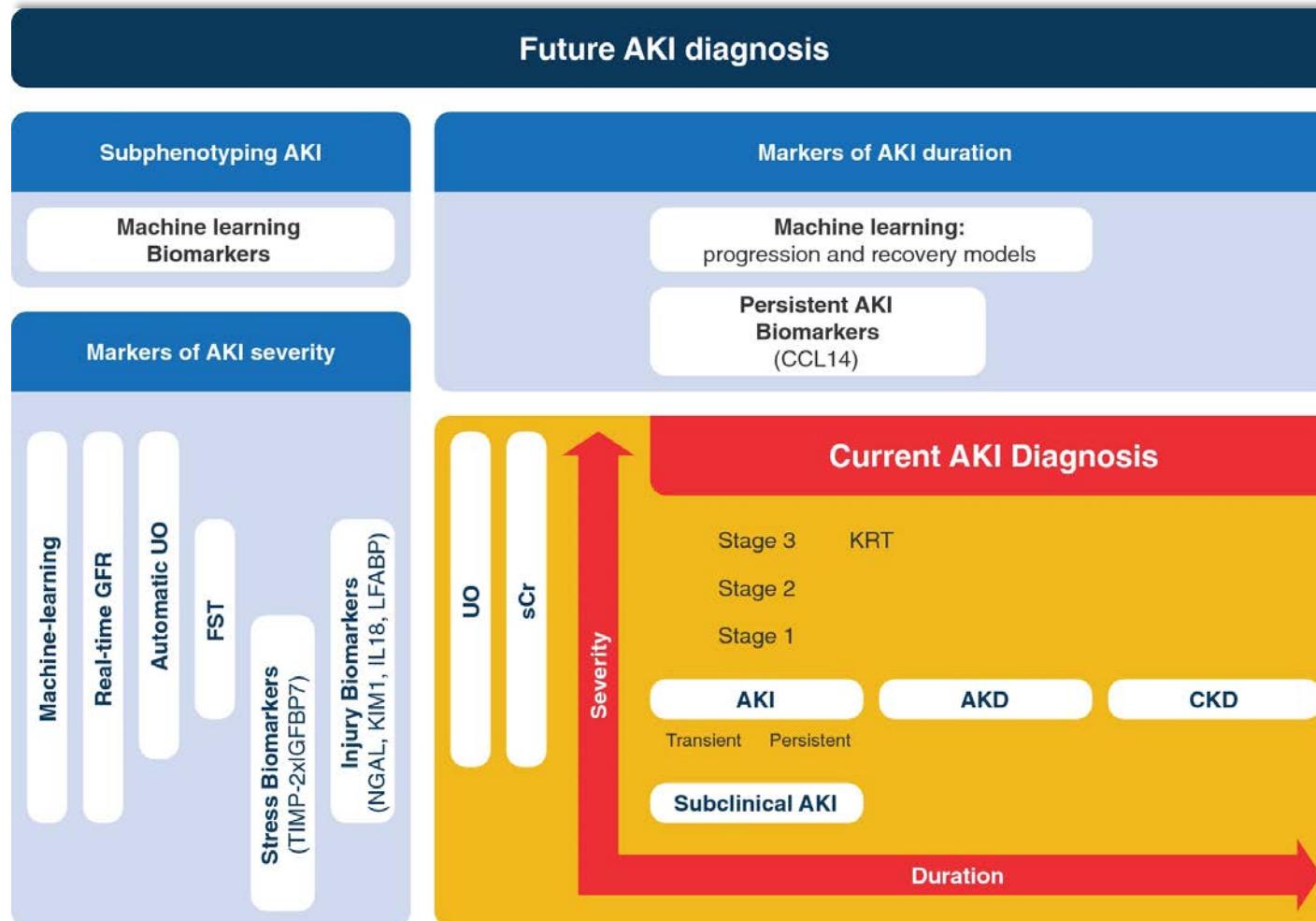
Table 2. Primary Outcome

	Control (n = 142)	Intervention (n = 136)	P value	OR (Intervention versus control) (95% CI)	RRR ^a (%) (95% CI)	ARR ^b (%) (95% CI)
Primary outcome						
Patients treated according to KDIGO bundle, no./total no. (%)	6/142 (4.2)	89/136 (65.4)	<.001	42.92 (17.61-104.60)	63.9 (54.4-71.4)	61.2 (52.6-69.9)
Discontinuation of nephrotoxic agents, no. (%)	120 (84.5)	134 (98.5)	<.001	12.28 (2.83-53.33)	90.5 (60.4-97.7)	14.0 (7.7-20.3)
Optimization of hemodynamic and perfusion pressure, no. (%)	76 (53.5)	97 (71.3)	.002	2.16 (1.31-3.55)	38.3 (15.2-55.1)	17.8 (6.6-29.0)
Close monitoring of serum creatinine and urine output, no. (%)	63 (44.4)	124 (91.2)	<.001	12.96 (6.57-25.54)	84.1 (72.2-90.9)	46.8 (37.4-56.3)
Avoidance of hyperglycemia, no. (%)	35 (24.6)	106 (77.9)	<.001	10.80 (6.19-18.85)	70.7 (59.3-78.9)	53.3 (43.4-63.2)
Consideration of alternatives to radio contrast agents, no. (%)	138 (97.2)	134 (98.5)	.440	1.94 (0.35-10.78)	47.8 (-180.4 to 90.3)	1.3 (-2.0 to 4.7)
Discontinuation of ACEi/ARBs, no. (%)	129 (90.8)	131 (96.3)	.064	2.64 (0.92-7.62)	59.8 (-9.6 to 85.3)	5.5 (-0.2 to 11.2)
Avoidance of HES, gelatine, chloride-rich solutions, no. (%)	124 (87.3)	130 (95.6)	.014	3.15 (1.21-8.18)	65.2 (14.9-85.8)	8.3 (1.8-14.7)
Median number of preventive measures, median (Q1, Q3)	5 (4, 6)	7 (6, 7)	<.001			2 (1-2)
Number of preventive measures, no. (%)			<.001			
1	0 (0)	0 (0)				
2	6 (4.2)	0 (0)				
3	9 (6.3)	2 (1.5)				
4	36 (25.4)	14 (10.3)				
5	50 (35.2)	15 (11.0)				
6	35 (24.6)	16 (11.8)				
7	6 (4.2)	89 (65.4)				

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Qu'attendre des années à venir



Mesure continue du DFG

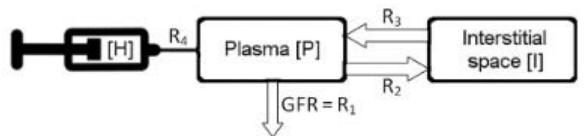
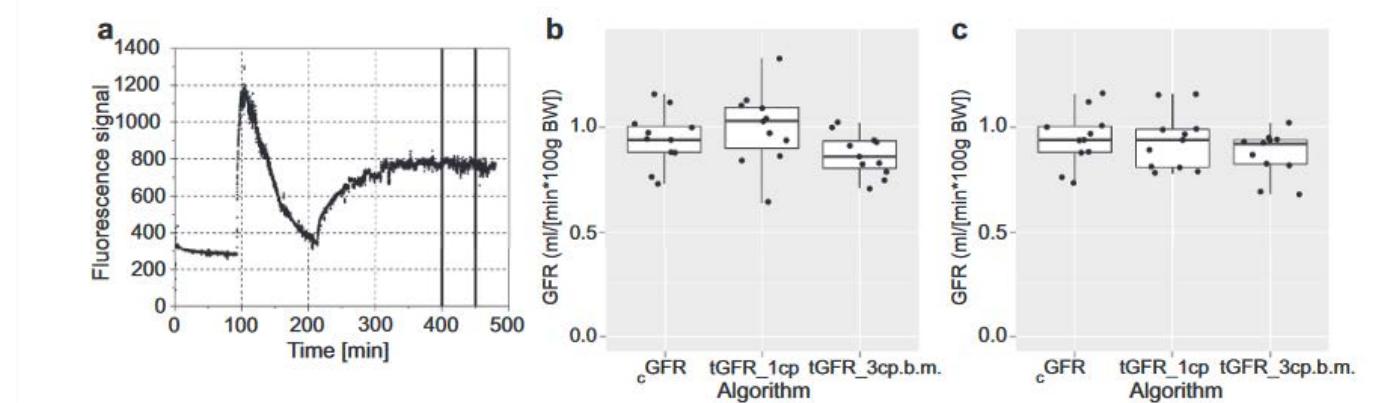
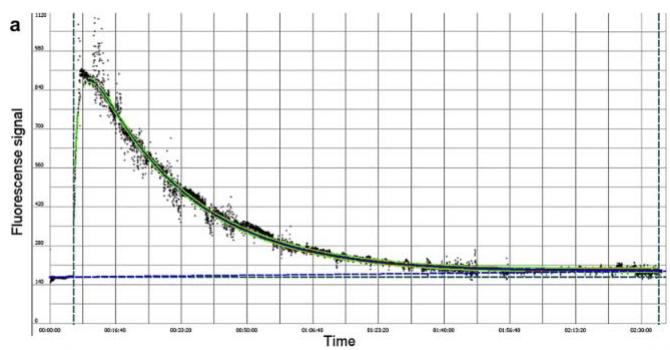


Figure 6 | Scheme of the adapted 3-compartment model
($t\text{-GFR}_{3\text{cp}}$). H, injection compartment; I, interstitial compartment; P, plasma compartment; R_1 - R_4 , diffusion or distribution rate constants.

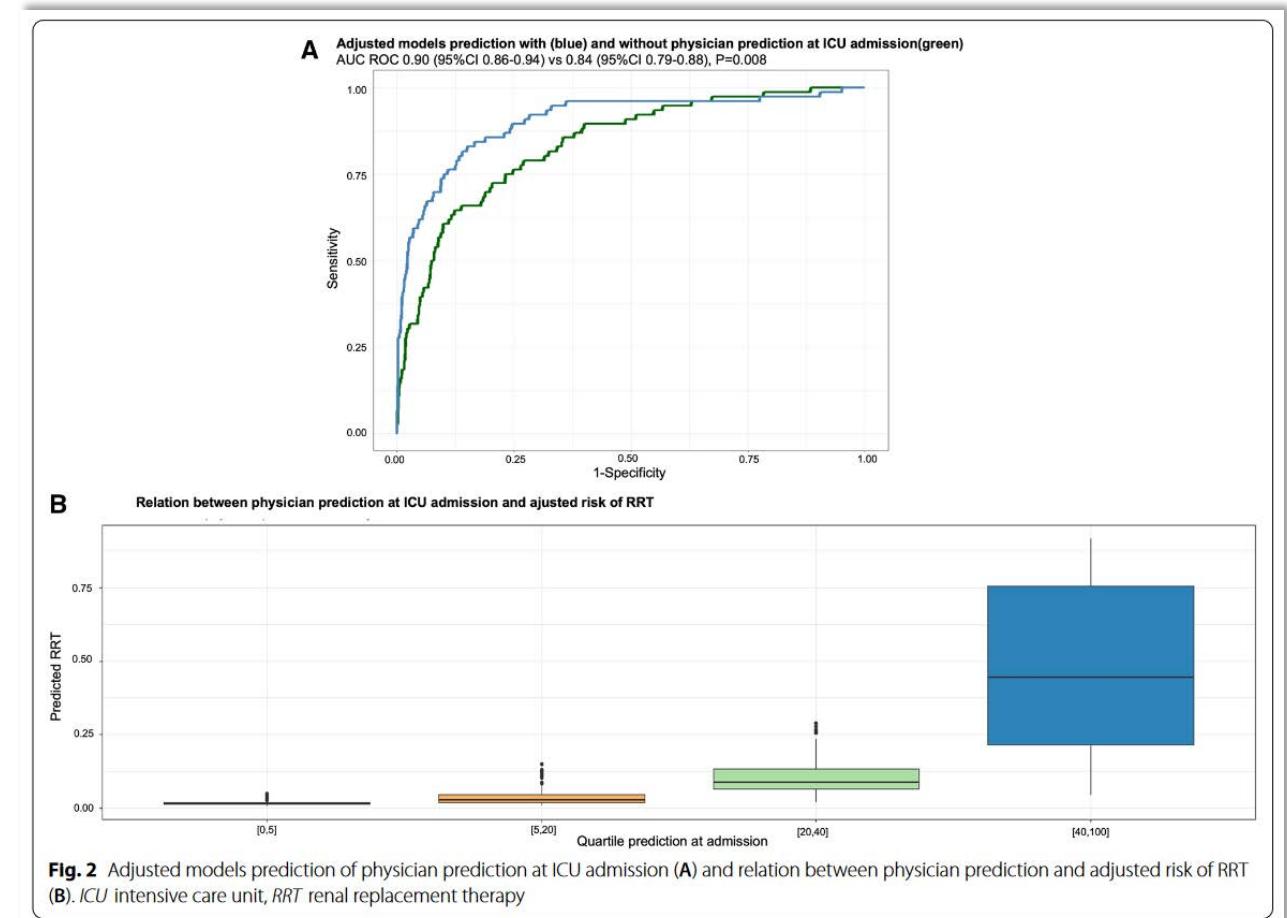


Réintroduire un peu de jugement clinique?

$$P(A|B) = \frac{P(B|A)P(A)}{P(B)}$$

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Evaluer la fonction rénale en pratique

1. Se fier aux marqueurs usuels de dysfonction rénale

a- La créatinine témoigne de l'état du rein dans les dernières heures



b- L'oligurie est le marqueur d'alerte

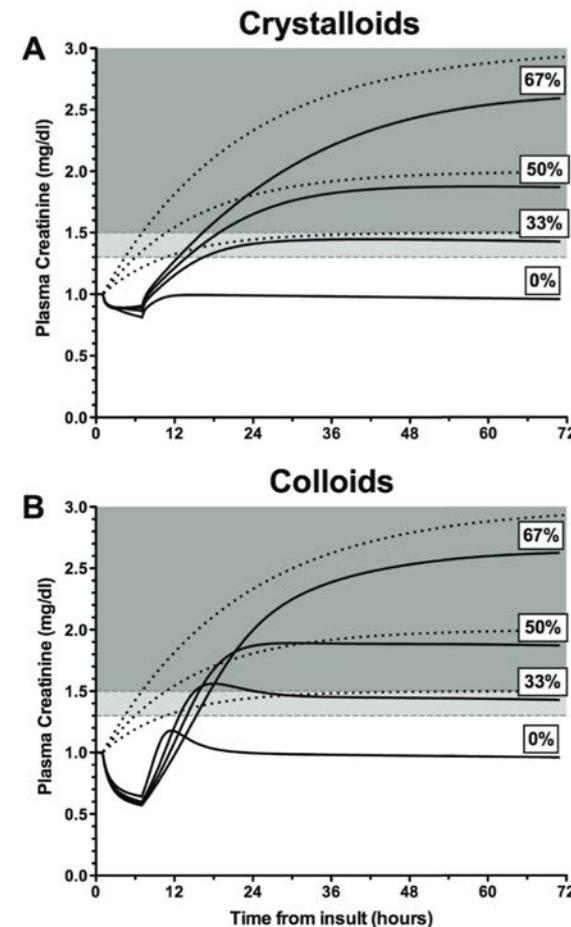
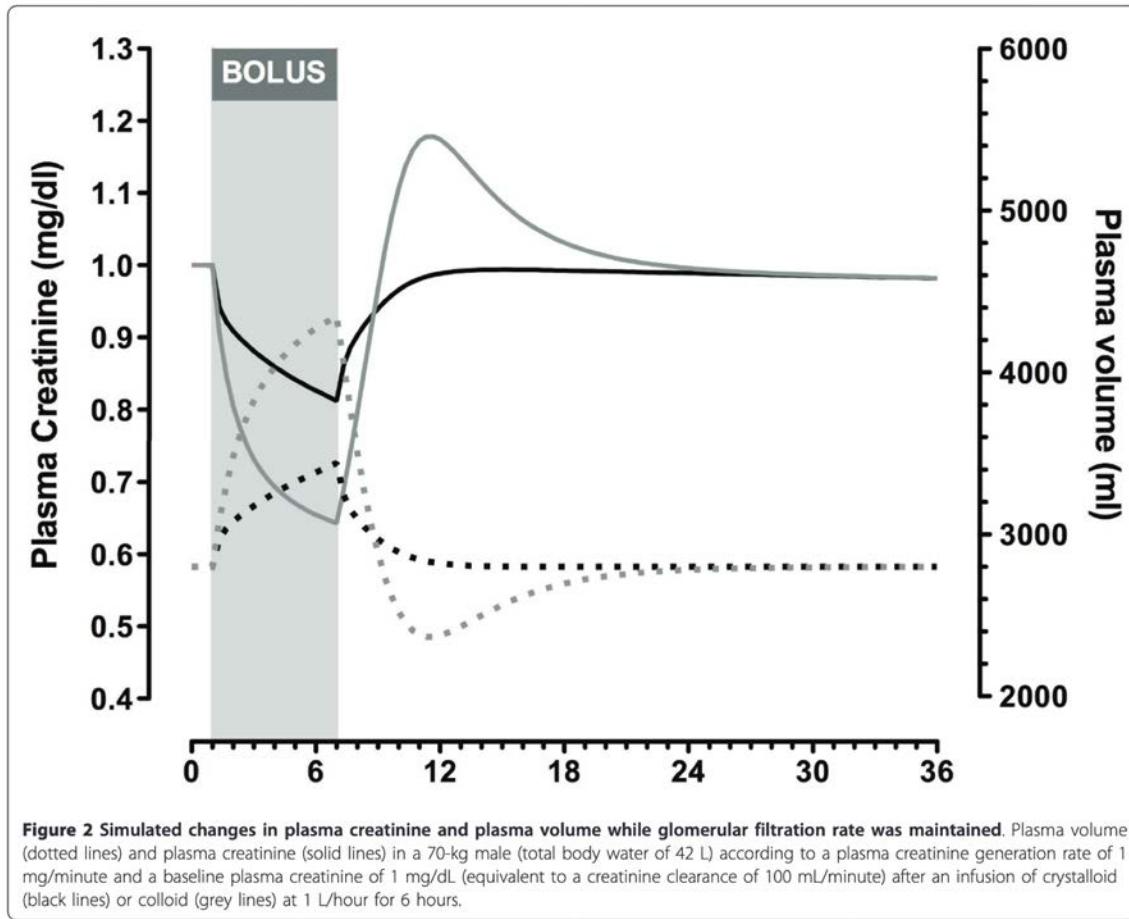


2. Pour le moment je n'utilise aucun biomarqueur...

3. Des avancées vont peut-être bouleverser notre façon de faire

4. Prenez en compte le contexte clinique

Exemple des solutés de remplissage



Thank you for your attention

