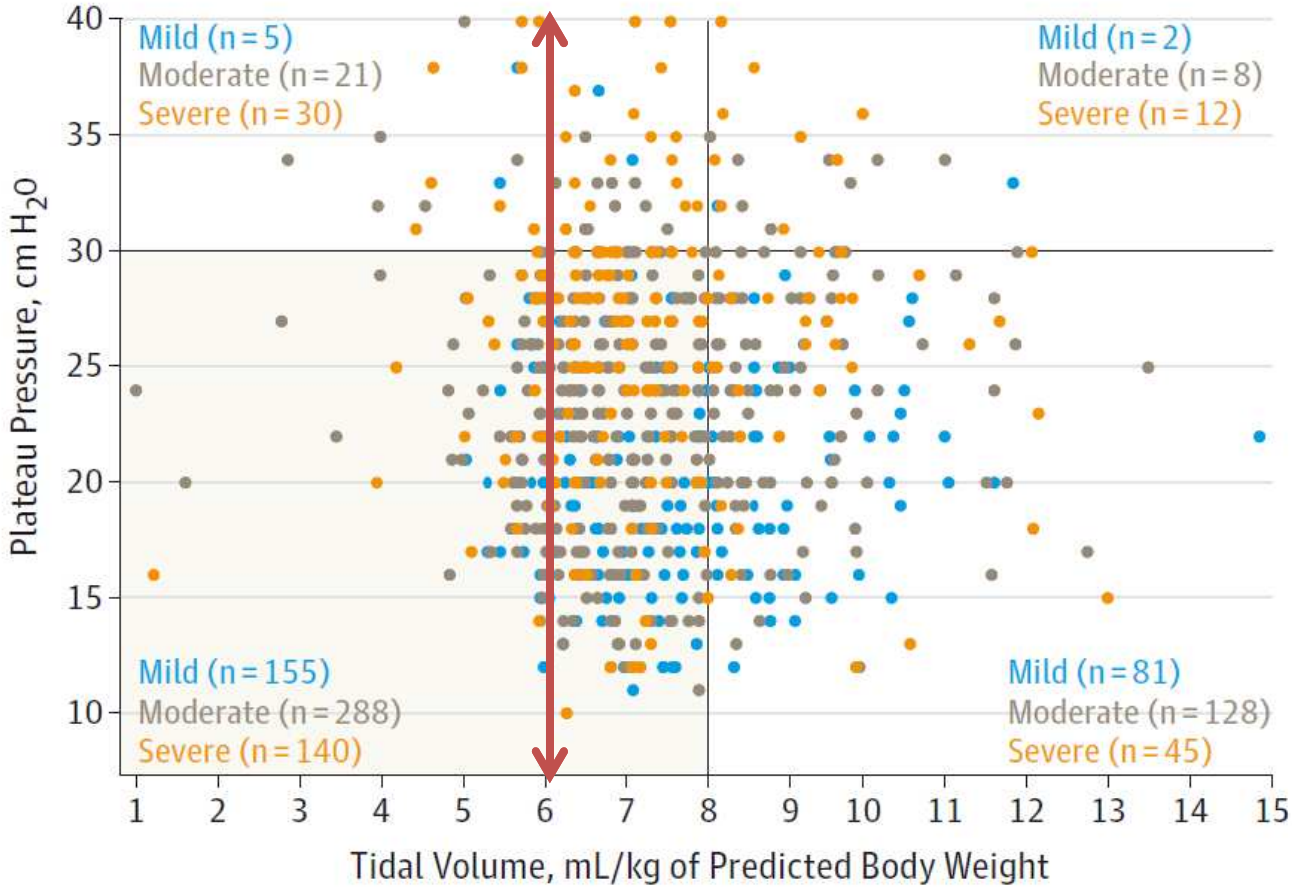
L’ article de l’année en réanimation

JARCA 2016

07/12/16

Nathan Ferrand SAR II

Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries



Bellani et al. JAMA. 2016

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit

Stéphane Gaudry, M.D., David Hajage, M.D., Fréderique Schortgen, M.D., Laurent Martin-Lefevre, M.D., Bertrand Pons, M.D., Eric Boulet, M.D., Alexandre Boyer, M.D., Guillaume Chevrel, M.D., Nicolas Lerolle, M.D., Ph.D., Dorothée Carpentier, M.D., Nicolas de Prost, M.D., Ph.D., Alexandre Lautrette, M.D., Anne Bretagnol, M.D., Julien Mayaux, M.D., Saad Nseir, M.D., Ph.D., Bruno Megarbane, M.D., Ph.D., Marina Thirion, M.D., Jean-Marie Forel, M.D., Julien Maizel, M.D., Ph.D., Hodane Yonis, M.D., Philippe Markowicz, M.D., Guillaume Thiery, M.D., Florence Tubach, M.D., Ph.D., Jean-Damien Ricard, M.D., Ph.D., and Didier Dreyfuss, M.D., for the AKIKI Study Group*

May 2016

INTRODUCTION

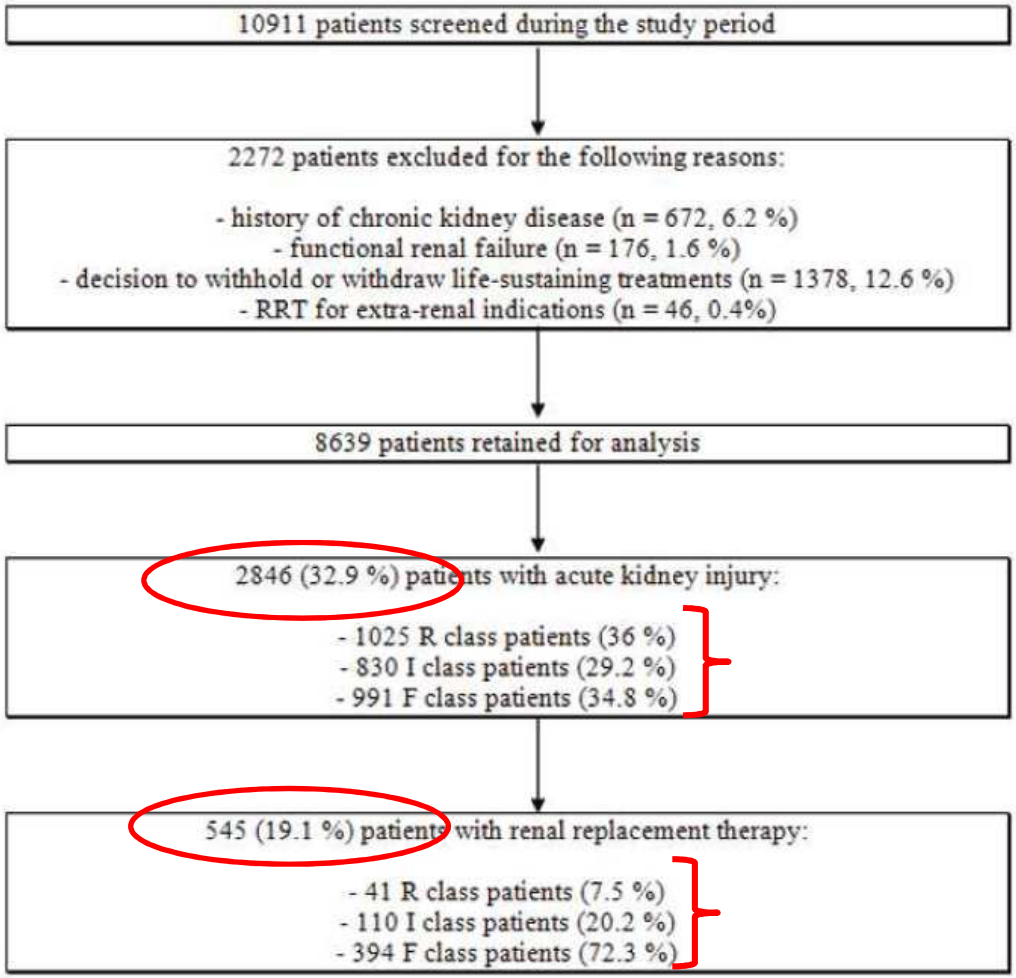


Figure 1 Study flow chart. RRT, renal replacement therapy; R class, Risk; I class, Injury; F class, Failure.

Clec'h et al. Critical Care 2011

INTRODUCTION

Table 4 Association of AKI with hospital mortality: results of the unadjusted and adjusted Fine and Gray models[a]

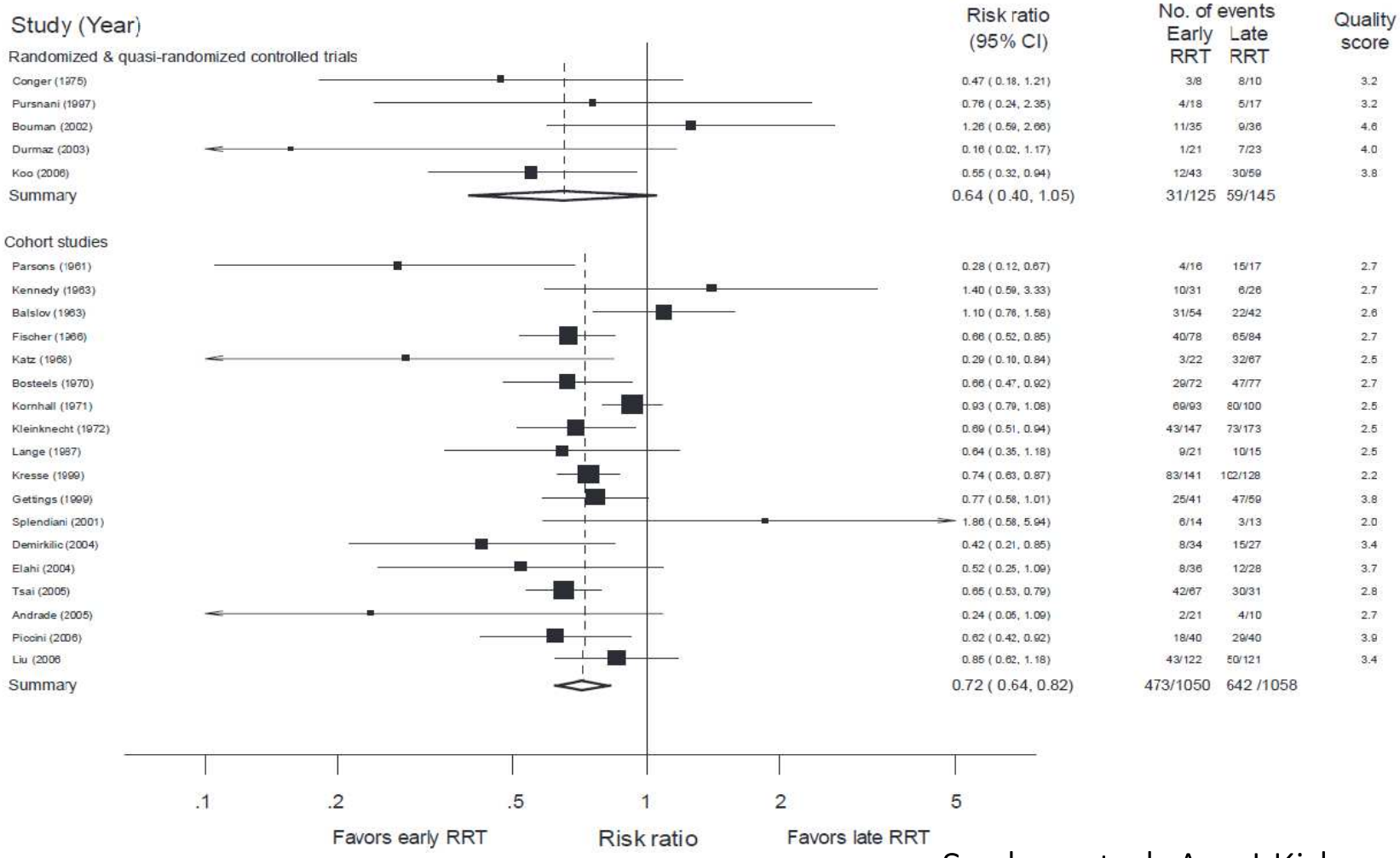
Variable	SHR univariate analysis (95% CI)	*P* value	SHR multivariate analysis (95% CI)	*P* value
No AKI	1	-	1	-
R class	2.28 (1.62 to 3.19)	<0.0001	1.58 (1.32 to 1.88)	<0.0001
I class	7.39 (5.37 to 10.17)	<0.0001	3.99 (3.43 to 4.65)	<0.0001
F class	9.73 (8.16 to 11.60)	<0.0001	4.12 (3.55 to 4.79)	<0.0001
Non-renal SOFA score, per point	-	-	1.19 (1.1.18 to 1.21)	<0.0001
McCabe class 3	-	-	2.71 (2.34 to 3.15)	<0.0001
Respiratory failure	-	-	3.08 (1.36 to 7.01)	<0.01

[a]SHR, sub-hazard ratio; 95% CI, 95% confidence interval; SOFA, Sequential Organ Failure Assessment; non-renal SOFA: SOFA renal component.

Clec'h et al. Critical Care 2011

INTRODUCTION

Timing of Renal Replacement Therapy Initiation in Acute Renal Failure: A Meta-analysis



Seabra et al. Am J Kidney Dis. 2008

INTRODUCTION

A comparison of early versus late initiation of renal replacement therapy in critically ill patients with acute kidney injury: a systematic review and meta-analysis

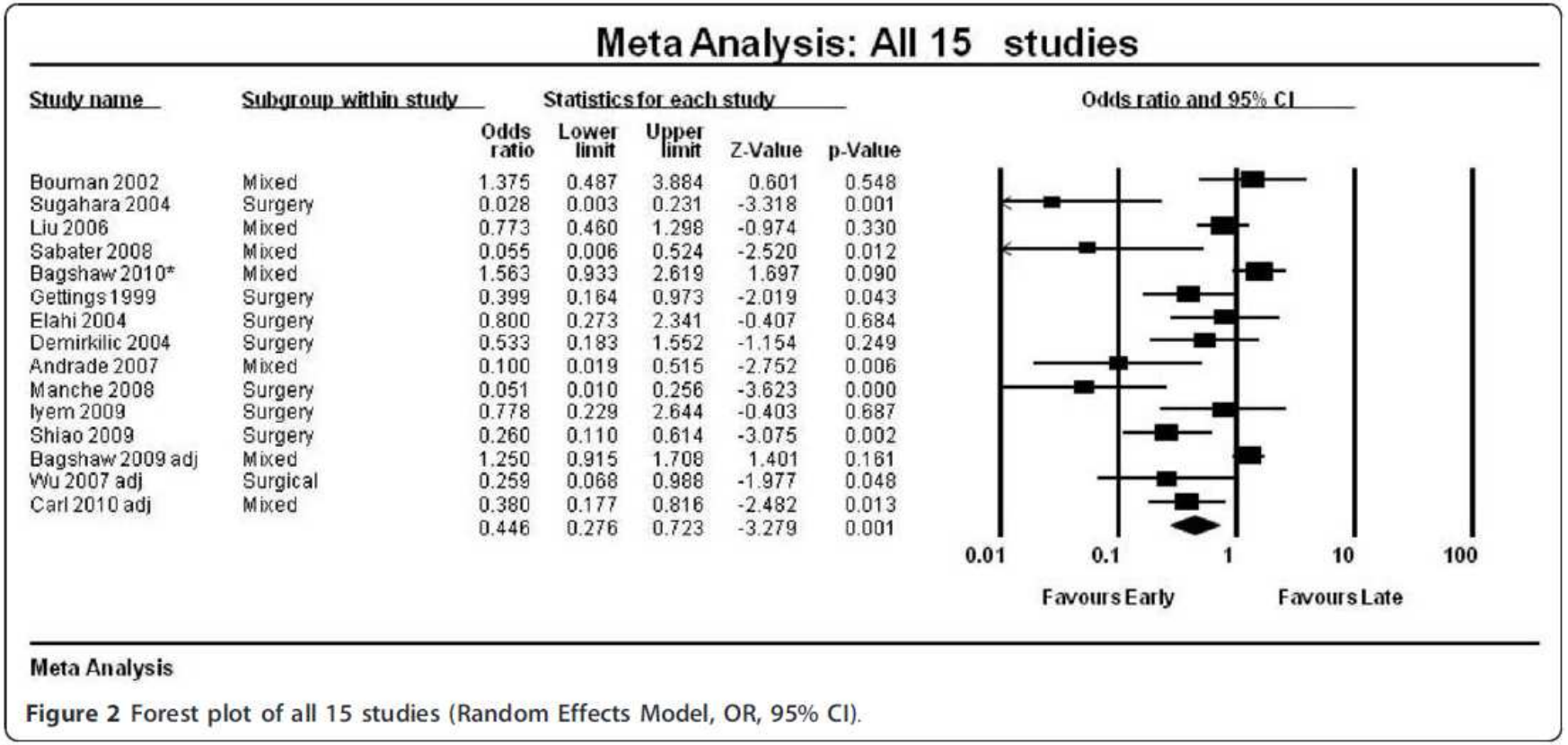
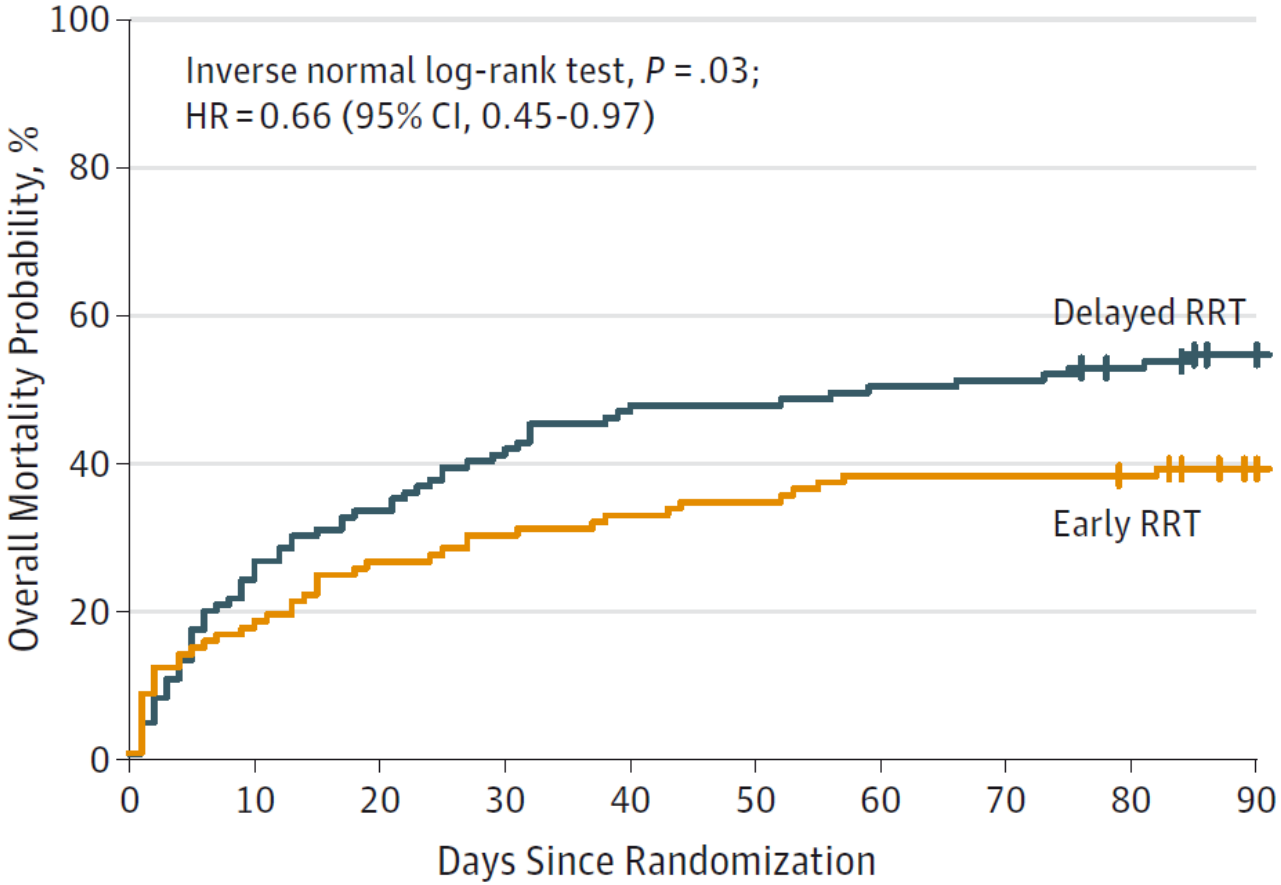


Figure 2 Forest plot of all 15 studies (Random Effects Model, OR, 95% CI).

Kervallas et al. Critical Care. 2011

INTRODUCTION

Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury
The ELAIN Randomized Clinical Trial



ELAIN Trial

Prospective Monocentrique

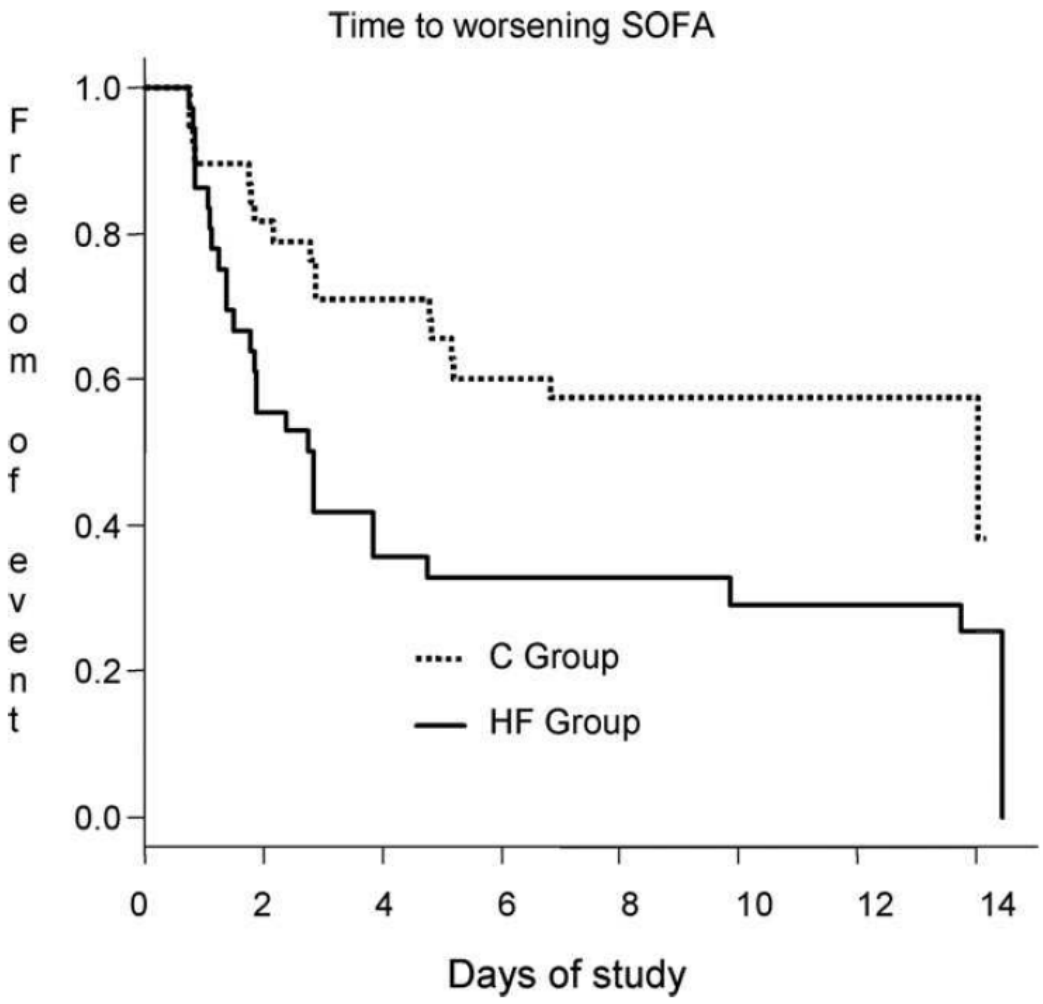
KDIGO 2 / NGAL > 150ng/ml

112 précoce vs 119 tardif

A.Zarbock et al. JAMA 2016

INTRODUCTION

Impact of continuous venovenous hemofiltration on organ failure during the early phase of severe sepsis: A randomized controlled trial*



D.Payen and al. crit care med 2009

INTRODUCTION

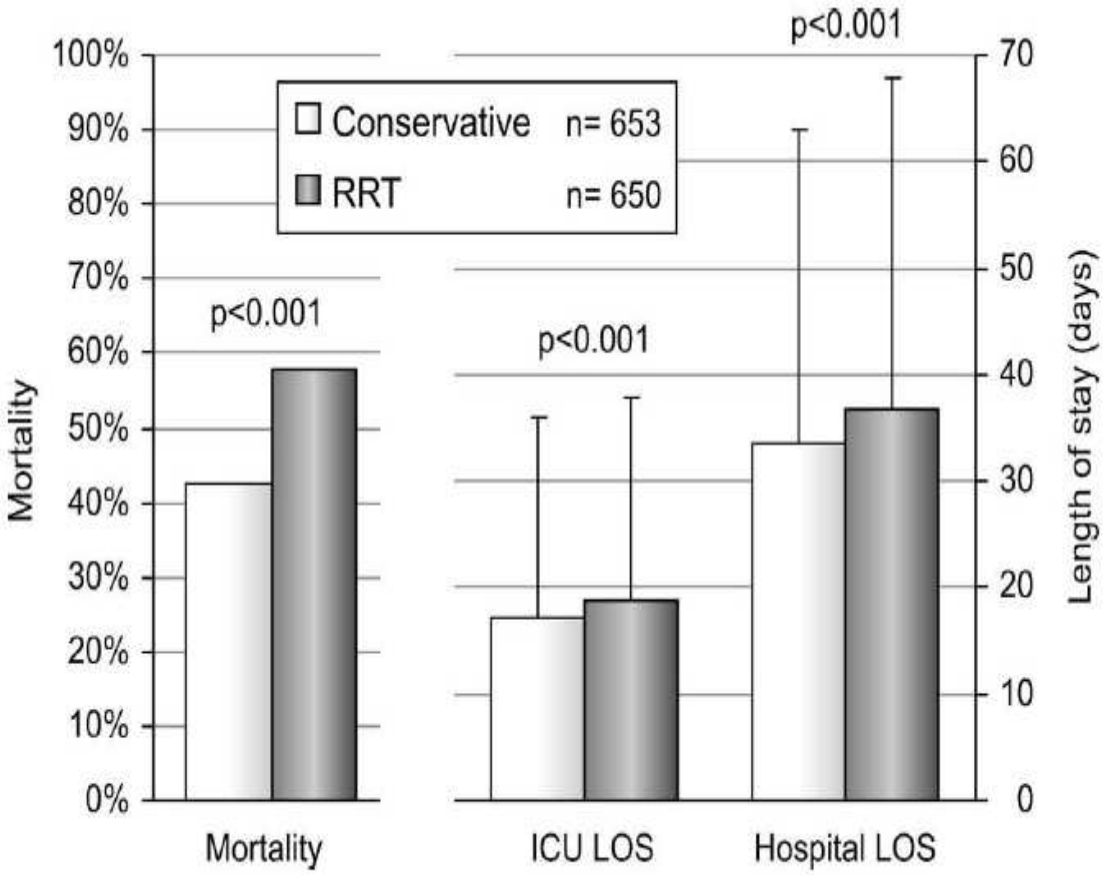


Figure 2 Outcome in patients with conservative treatment and renal replacement therapy. LOS, length of stay; RRT, renal replacement therapy.

M.Elseviers et al. Critical care 2010

INTRODUCTION

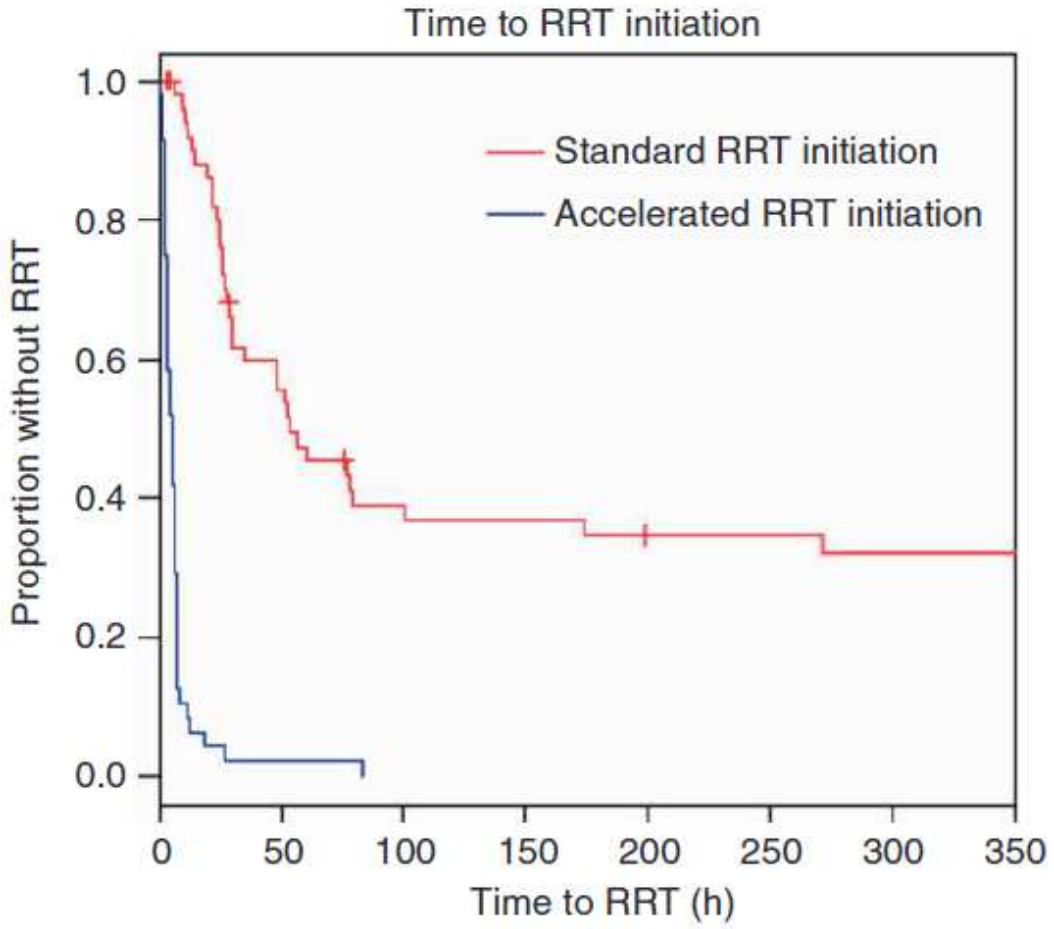


Figure 2 | Time from eligibility to renal replacement therapy (RRT) initiation stratified by treatment strategy ($P < 0.0001$).

Wald et al. Kidney Int. 2015

INTRODUCTION

Renal replacement therapy in adult and pediatric intensive care

Recommendations by an expert panel from the French Intensive Care Society (SRLF) with the French Society of Anesthesia Intensive Care (SFAR) French Group for Pediatric Intensive Care Emergencies (GFRUP) the French Dialysis Society (SFD)

1.1 RRT should be initiated without delay in lifethreatening situations (hyperkalemia, metabolic acidosis, tumor lysis syndrome, refractory pulmonary edema). (Expert opinion)

Strong agreement

1.2 The available data are insufficient to define optimal timing of initiation of RRT outside life-threatening situations. (Expert opinion)

Strong agreement

Vinsonneau et al. Ann.Intensive care. 2015

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit

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May 2016

MATERIEL et METHODE

➢ OBJECTIF

Evaluer l'impact sur la mortalité à J60 d'une initiation précoce ou tardive de l'EER chez des patients de réanimation en insuffisance rénale aigüe

MATERIEL et METHODE

- Etude prospective multicentrique randomisée dans 31 réanimations françaises

- Septembre 2013 à Janvier 2016

MATERIEL et METHODE

➢ INCLUSION

- ✓ Adulte, admission en réanimation avec une IRA
- ✓ Ventilation mécanique et/ou Noradrénaline
- ✓ AKI KDIGO 3

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline OR $\geqslant$0.3 mg/dl ($\geqslant$26.5 μmol/l) increase	$<$0.5 ml/kg/h for 6–12 hours
2	2.0–2.9 times baseline	$<$0.5 ml/kg/h for $\geqslant$12 hours
3	3.0 times baseline OR Increase in serum creatinine to $\geqslant$4.0 mg/dl ($\geqslant$353.6 μmol/l) OR Initiation of renal replacement therapy OR, In patients $<$18 years, decrease in eGFR to $<$35 ml/min per 1.73 m^2	$<$0.3 ml/kg/h for $\geqslant$24 hours OR Anuria for $\geqslant$12 hours

MATERIEL et METHODE

➢ EXCLUSION

- ➢ Critère d'épuration extra rénale en urgence
- ✓ Urée ≥ 40mmol/L
- ✓ Kaliémie ≥ 6mmol/L ou ≥ 5,5mmol/L sous traitement
- ✓ Acidose métabolique avec pH < 7,15
- ✓ OAP de surcharge avec hypoxémie

MATERIEL et METHODE

➢ EXCLUSION

- Insuffisance rénale chronique (cl < 30ml/min), greffé rénal ou antécédents d'épuration extra rénale
- Patient ayant des critères d'inclusions mais non randomisés dans le 5 heures
- AKI n'étant pas des nécroses tubulaires aigües à priori
- Cirrhose Child C
- ACR sans signe de réveil
- LATA ou décès attendu dans les 24 heures

MATERIEL et METHODE

➢ RANDOMISATION

- ✓ Bloc
- ✓ Stratifiée par centre
- ✓ Ratio 1:1
- ✓ Dans les 5 heures suivant le diagnostic d'AKI stade 3

MATERIEL et METHODE

➢ Groupe PRECOCE

- ✓ Initiation de l'épuration dans les 6 heures suivant le diagnostic d'AKI stade 3 (randomisation dans les 5 heures)

MATERIEL et METHODE

➢Groupe TARDIF

Table S1. Criteria mandating RRT initiation in the delayed RRT strategy group*
Oliguria or anuria for more than 72 hours after randomization
Blood urea nitrogen of more than 112 md/dl (40 mmol/liter)
Serum potassium concentration of more than 6 mmol/liter
Serum potassium concentration of more than 5.5 mmol/liter despite medical treatment (bicarbonate and/or glucose-insulin infusion)
pH below 7.15 in a context of pure metabolic acidosis ($PaCO_2$ below 35 mmHg) or in a context of mixed acidosis with $PaCO_2$ of 50 mmHg or more without possibility of increasing alveolar ventilation
Acute pulmonary edema due to fluid overload responsible for severe hypoxemia requiring oxygen flow rate of more than 5 l/min to maintain an SpO_2 of more than 95% or requiring an FiO_2 greater than 50% in patients already on invasive or non-invasive mechanical ventilation and despite diuretic therapy

MATERIEL et METHODE

➢ EPURATION

- ➢ Choix de la technique, des modalités, de l'anticoagulation laissé à la discrétion des cliniciens

- ➢ Sevrage de l'épuration si diurèse spontanée ≥ 500ml/24h ou ≥2000ml/24 avec diurétique

- ➢ Reprise de l'épuration
- ✓ diurèse ≤ 1000ml/24h ou ≤ 2000ml/24h avec diurétique
- ✓ pas de baisse spontanée de la créatininémie

Critères de jugement secondaire

- ✓ Recours à l'épuration dans le groupe Tardif
- ✓ Le nombre de jours sans épuration, sans cathéter de dialyse, sans ventilation mécanique, sans noradrénaline
- ✓ SOFA J3 et J7
- ✓ Mortalité J28
- ✓ Durée de séjour
- ✓ LATA
- ✓ Complications de l'AKI ou de l'épuration

MATERIEL et METHODE

➢ STATISTIQUE

- Analyse en intention de traité
- Mortalité attendue à J60 de 55%
- Etude de supériorité avec l'hypothèse d'une réduction de 15% de la mortalité dans le groupe Tardif
- Risque α 5%
- Puissance 90%

546 Patients

RESULTATS

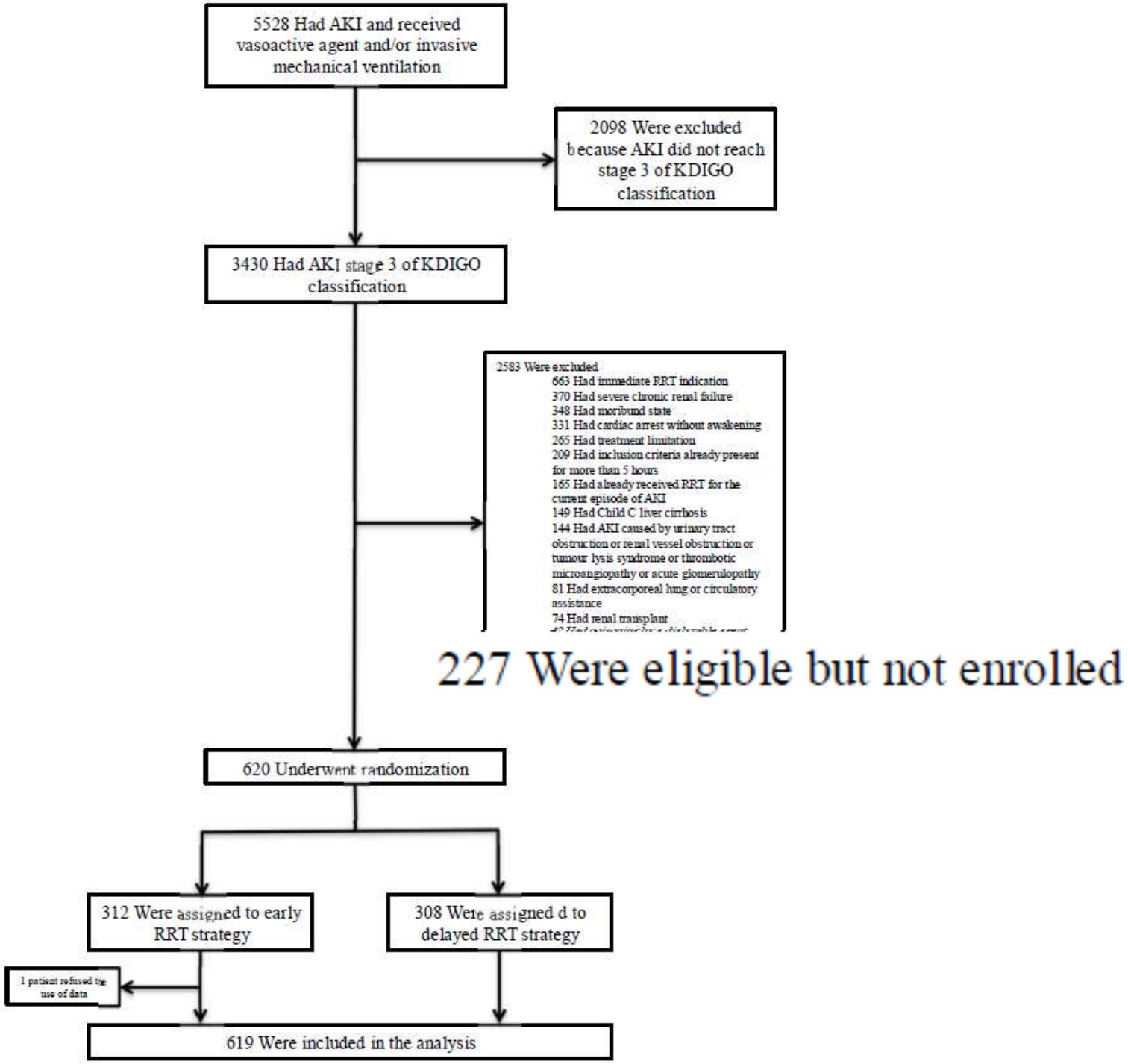
5528 Had AKI and received vasoactive agent and/or invasive mechanical ventilation
2098 Were excluded because AKI did not reach stage 3 of KDIGO classification
3430 Had AKI stage 3 of KDIGO classification
2583 Were excluded
663 Had immediate RRT indication
370 Had severe chronic renal failure
348 Had moribund state
331 Had cardiac arrest without awakening
265 Had treatment limitation
209 Had inclusion criteria already present for more than 5 hours
165 Had already received RRT for the current episode of AKI
149 Had Child C liver cirrhosis
144 Had AKI caused by urinary tract obstruction or renal vessel obstruction or tumour lysis syndrome or thrombotic microangiopathy or acute glomerulopathy
81 Had extracorporeal lung or circulatory assistance
74 Had renal transplant
227 Were eligible but not enrolled
620 Underwent randomization
312 Were assigned to early RRT strategy
308 Were assigned d to delayed RRT strategy
1 patient refused the use of data
619 Were included in the analysis

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Early Strategy (N=311)	Delayed Strategy (N=308)
Age — yr	64.8±14.2	67.4±13.4
Serum creatinine before ICU admission — mg/dl†	0.95±0.26	0.97±0.31
Coexisting conditions — no. (%)		
Chronic renal failure	22 (7)	38 (12)
Hypertension	161 (52)	167 (54)
Diabetes mellitus	82 (26)	81 (26)
Congestive heart failure	24 (8)	32 (10)
Ischemic heart disease	30 (10)	32 (10)
SAPS III at enrollment‡	72.6±14.4	73.7±14.2
SOFA score at enrollment§	10.9±3.2	10.8±3.1
Exposure to at least one nephrotoxic agent in past 2 days — no./total no. (%)¶	194/311 (62)	195/308 (63)
Intravenous contrast	66/194 (34)	71/195 (36)
Aminoglycoside	106/194 (55)	106/195 (54)
Vancomycin	26/194 (13)	29/195 (15)
Physiological support — no. (%)		
Invasive mechanical ventilation	266 (86)	267 (87)
Vasopressor support with epinephrine or norepinephrine	265 (85)	263 (85)
Sepsis status — no. (%)‖		
Sepsis	25 (8)	21 (7)
Severe sepsis	16 (5)	19 (6)
Septic shock	209 (67)	204 (66)
Patients with oliguria or anuria — no. (%)	202 (65)	191 (62)
Serum creatinine — mg/dl	3.25±1.40	3.20±1.32
Blood urea nitrogen — mg/dl	53±24	54±24
Serum potassium — mmol/liter	4.4±0.7	4.4±0.7
Serum bicarbonate — mmol/liter	18.7±5.1	18.8±5.5

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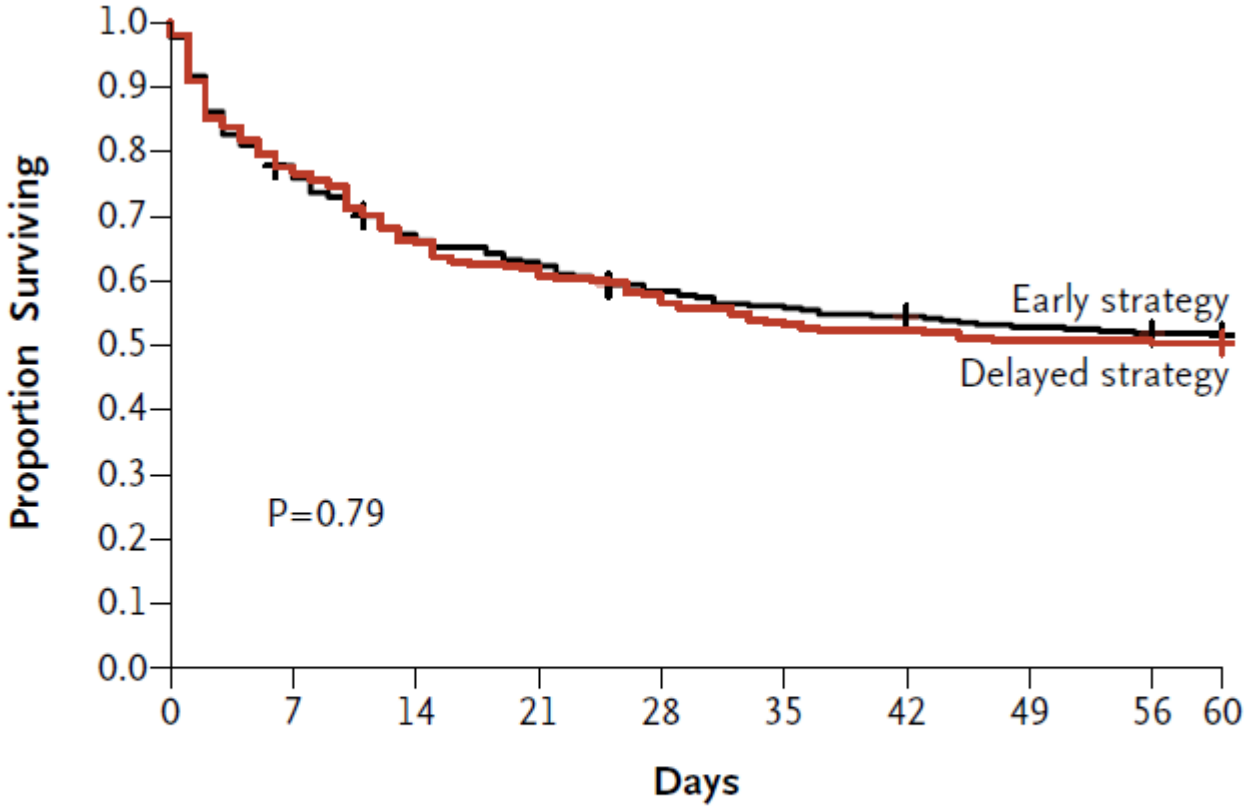

48,5%

49,7%

No. at Risk

Early strategy	311	241	207	194	179	172	167	161	158	157
Delayed strategy	308	239	204	191	178	165	161	156	156	155

Table 2. Primary and Secondary Outcomes and Adverse Events.*

Outcome	Early Strategy (N=311)	Delayed Strategy (N=308)	P Value	Hazard Ratio (95% CI)
Death — no. (% [95% CI])†				
Day 28	129 (41.6 [35.9–46.9])	134 (43.5 [37.7–48.8])		
Day 60	150 (48.5 [42.6–53.8])	153 (49.7 [43.8–55.0])	0.79	1.03 (0.82–1.29)
Adjusted analysis‡			0.84	1.02 (0.81–1.29)
Patients with treatment limitation in ICU — no. (%)§	71 (23)	73 (24)	0.78	
Median study day on which a treatment limitation first occurred (IQR)§	6 (2–12.5)	8 (3–14)	0.23	
Patients who received renal-replacement therapy — no. (%)	305 (98)	157 (51)	<0.001	
Median renal-replacement therapy–free days (IQR)	17 (2–26)	19 (5–29)	<0.001	
Median mechanical ventilation–free days (IQR)	7 (0–22)	6 (0–21)	0.76	
Median vasopressor-free days (IQR)	20 (1–26)	20 (0–26)	0.67	
SOFA score				
Day 3	10±4	10±4	0.14	
Day 7	8±4	8±4	0.63	
SOFA score without renal component				
Day 3	8±4	8±4	0.62	
Day 7	6±4	6±3	0.94	
Median length of ICU stay (IQR)				
Survivors	13 (8–23)	13 (7–23)	0.87	
Nonsurvivors	6 (2–14)	6 (2–13)	0.92	
Median length of hospital stay (IQR)				
Survivors	29 (17–51)	32 (20–51)	0.58	
Nonsurvivors	6 (2–14)	6 (2–13)	0.85	
Nosocomial infection				
Catheter-related bloodstream infection				
Patients with infection — no. (%)¶	31 (10)	16 (5)	0.03	
Median incidence per 1000 catheter-days (IQR)	3.4 (2.3–4.6)	2.1 (1.1–3.1)	0.09	
Unexplained bloodstream infection — no. (%)	21 (7)	26 (8)	0.43	
Ventilator-associated pneumonia — no. (%)	50 (16)	37 (12)	0.15	
Dependence on renal-replacement therapy — no./total no. (%)				
Day 28	22/179 (12)	17/178 (10)	0.51	
Day 60	3/157 (2)	8/155 (5)	0.12	

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Death — no. (% [95% CI])†				
Day 28	129 (41.6 [35.9–46.9])	134 (43.5 [37.7–48.8])		
Day 60	150 (48.5 [42.6–53.8])	153 (49.7 [43.8–55.0])	0.79	1.03 (0.82–1.29)
Adjusted analysis‡			0.84	1.02 (0.81–1.29)
Patients with treatment limitation in ICU — no. (%)§	71 (23)	73 (24)	0.78	
Median study day on which a treatment limitation first occurred (IQR)§	6 (2–12.5)	8 (3–14)	0.23	
Patients who received renal-replacement therapy — no. (%)	305 (98)	157 (51)	<0.001	
Median renal-replacement therapy–free days (IQR)	17 (2–26)	19 (5–29)	<0.001	
Median mechanical ventilation–free days (IQR)	7 (0–22)	6 (0–21)	0.76	
Median vasopressor-free days (IQR)	20 (1–26)	20 (0–26)	0.67	
SOFA score				
Day 3	10±4	10±4	0.14	
Day 7	8±4	8±4	0.63	
SOFA score without renal component				
Day 3	8±4	8±4	0.62	
Day 7	6±4	6±3	0.94	
Median length of ICU stay (IQR)				
Survivors	13 (8–23)	13 (7–23)	0.87	
Nonsurvivors	6 (2–14)	6 (2–13)	0.92	
Median length of hospital stay (IQR)				
Survivors	29 (17–51)	32 (20–51)	0.58	
Nonsurvivors	6 (2–14)	6 (2–13)	0.85	
Nosocomial infection				
Catheter-related bloodstream infection				
Patients with infection — no. (%)¶	31 (10)	16 (5)	0.03	
Median incidence per 1000 catheter-days (IQR)	3.4 (2.3–4.6)	2.1 (1.1–3.1)	0.09	
Unexplained bloodstream infection — no. (%)	21 (7)	26 (8)	0.43	
Ventilator-associated pneumonia — no. (%)	50 (16)	37 (12)	0.15	
Dependence on renal-replacement therapy — no./total no. (%)				
Day 28	22/179 (12)	17/178 (10)	0.51	
Day 60	3/157 (2)	8/155 (5)	0.12	

Table S5. Characteristics of RRT sessions delivered during the 28 days following randomization*

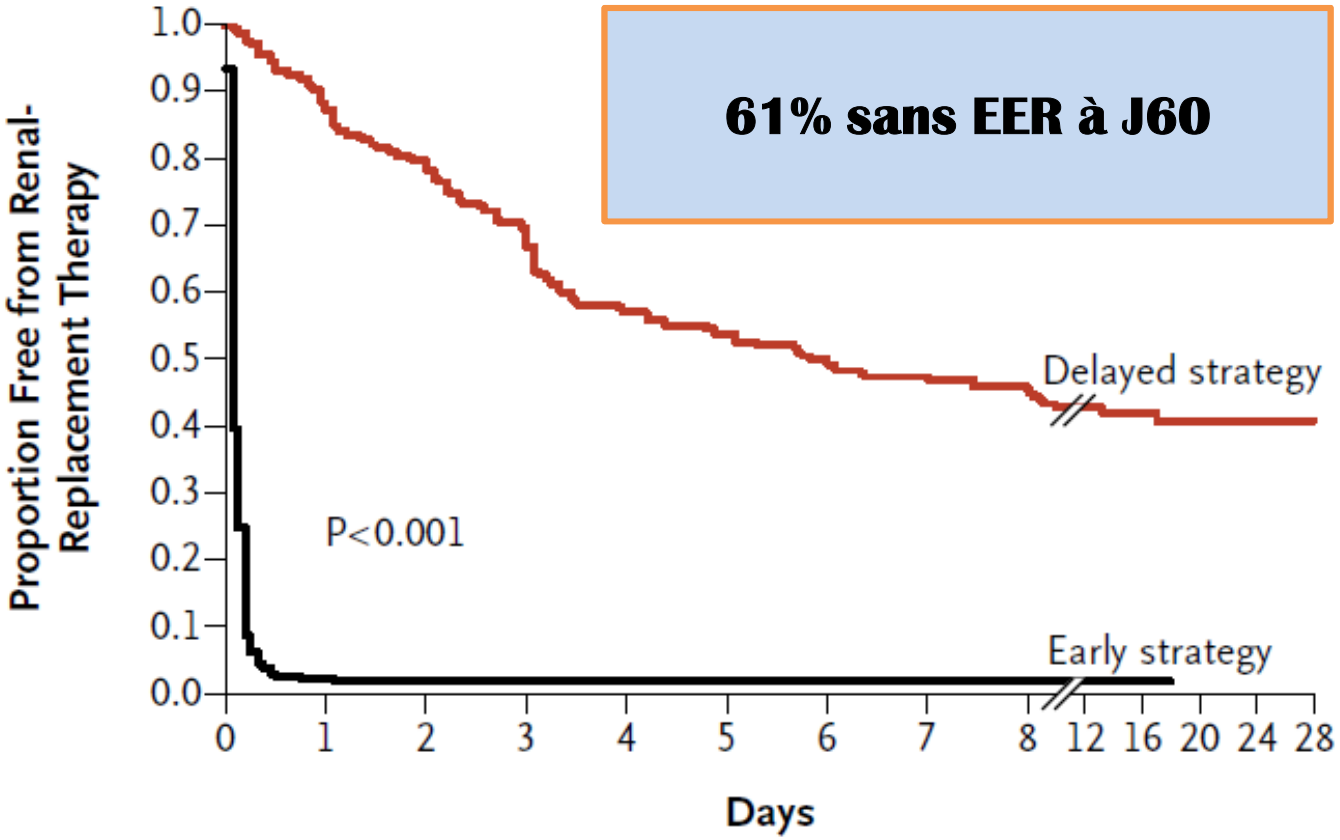
Characteristic	Early RRT strategy N=305	Delayed RRT strategy N=157	P Value
Dialysis catheter insertion site – no. (%)			0.81
Jugular	123 (41)	68 (44)	
Femoral	167 (55)	81 (52)	
Sub-clavian	13 (4)	7 (5)	
First modality– no. (%)			0.97
Intermittent RRT	169 (56)	86 (55)	
Continuous RRT	135 (44)	71 (45)	
RRT modalities during ICU stay– no. (%)			0.62
Intermitent RRT only	142 (47)	73 (47)	
Continuous RRT only	101 (33)	47 (30)	
Both modalities (intermittent and continuous)	61 (20)	37 (24)	
Mean blood urea nitrogen during RRT – mg/dl	38 (17)	57 (27)	<0.001
Total number of RRT sessions	1665	943	
Number of RRT sessions–median (IQR)†			
All patients at day 60	3 (2-7)	4 (2-8)	0.15
Patients dead at day 60	3 (2-7)	3 (2-7)	0.80
Patients alive at day 60	3 (1-8)	6 (3-10)	0.009
Resumption of RRT after initial cessation– no. (%)	11 (4)	4 (3)	0.54

Délai médian
2 vs 57 h

Table S7. Medical treatment of AKI-related metabolic complication before the first RRT session for patients who received it or during the whole ICU stay for patients who did not receive it

Characteristic	Early RRT strategy n=311	Delayed RRT strategy n=308	P Value
Diuretics– no. (%)	4 (1.3)	112 (36.5)	<0.001
Medical treatment of hyperkalemia – no. (%)	17 (5.5%)	67 (22.9%)	<0.001
Medical treatment of acidosis– no. (%)	21 (6.8%)	49 (16.7%)	<0.001

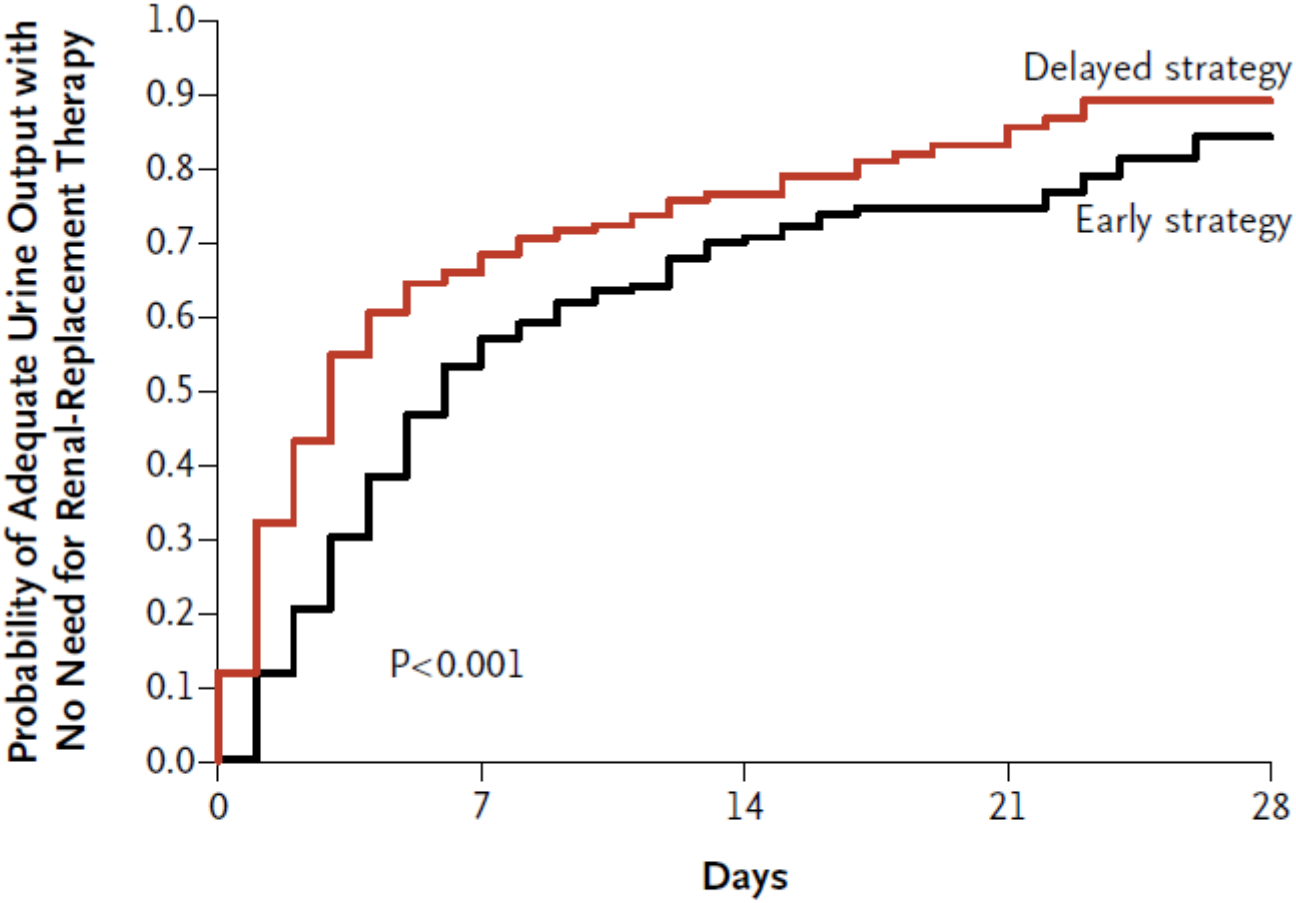
Table S3. Distribution of criteria which mandated RRT initiation in the delayed strategy group* (157 patients of 308 in this group actually received RRT)	
Criteria	
Oliguria or anuria for more than 72 hours after randomization – no. (%)	59 (38)
Blood urea nitrogen of more than 112 md/dl (40 mmol/liter) – no. (%)	59 (38)
Serum potassium concentration of more than 6 mmol/liter or more than 5.5 mmol/liter despite medical treatment (bicarbonate and/or glucose-insulin infusion) – no. (%)	27 (17)
pH below 7.15 in a context of pure metabolic acidosis ($PaCO_2$<35 mmHg) or in a context of mixed acidosis with $PaCO_2$ of 50 mmHg or more without possibility of increasing alveolar ventilation – no. (%)	33 (21)
Acute pulmonary edema due to fluid overload leading to severe hypoxemia requiring oxygen flow rate of more than 5 l/min to maintain SpO_2 of more than 95% or requiring an FiO_2 greater than 50% in patients already on invasive or non-invasive mechanical ventilation and despite diuretic therapy – no. (%)	9 (6)
Others	5 (3)



49%

No. at Risk

Early strategy	311	7	4	4	4	4	3	3	3	1	1	0	0	0
Delayed strategy	308	268	229	192	153	135	118	105	92	61	39	28	21	13



No. at Risk

Early strategy	311	99	42	27	10
Delayed strategy	308	68	29	14	7

DISCUSSION

DISCUSSION

➢ LES POINTS FORTS

- ✓ Etude randomisée contrôlée multicentrique, 2 analyses intermédiares
- ✓ Question posée pertinente
- ✓ Population grave, représentative de la réanimation
- ✓ AKI sévère
- ✓ Critère de Jugement « fort »
- ✓ Différence réelle délai EER, 2 vs 57h

DISCUSSION

➢ LIMITES

✓ EER d'IRA fonctionnelle dans le groupe précoce

- Les 2 groupes étant identiques…
- Aucunes données sur l'optimisation hémodynamique
- Pas de ionogrammes urinaires

TROP PRECOCE

✓ Stratification KDIGO

DISCUSSION

➢ LIMITES

- ✓ Mortalité hétérogène

p<0.001

- o 37,1% Groupe Tardif non épuré
- o 48,5% Groupe Précoce
- o 61,8% Groupe Tardif épuré

TROP TARDIF????

DISCUSSION

Variables	Early RRT strategy	Delayed RRT strategy-RRT-	Delayed RRT strategy- RRT+	Total
SAPS III at baseline				
Med [IQR]	71 [64-79]	72 [64-79]	73 [67-82.75]	72 [64-81]
Moy (std)	72.6 (14.41)	72.35 (14.26)	74.96 (13.68)	73.14 (14.21)
P value p value: 0.0684 (Kruskal-Wallis rank sum test)				
SAPS III at baseline (groups)				
< 70	130 (43.2%)	60 (42.3%)	53 (35.3%)	243 (41%)
>=70	171 (56.8%)	82 (57.7%)	97 (64.7%)	350 (59%)
Total	301 (50.8%)	142 (23.9%)	150 (25.3%)	593 (100%)
p value: 0.2618 (Pearson's Chi-squared test)				
SOFA at baseline				
Med [IQR]	11 [9-13]	10 [8-12]	12 [9-14]	11 [9-13]
Moy (std)	10.92 (3.18)	9.96 (2.89)	11.66 (3.12)	10.88 (3.15)
p value: <0.0001 (Kruskal-Wallis rank sum test)				

DISCUSSION

MONOCENTRIQUE

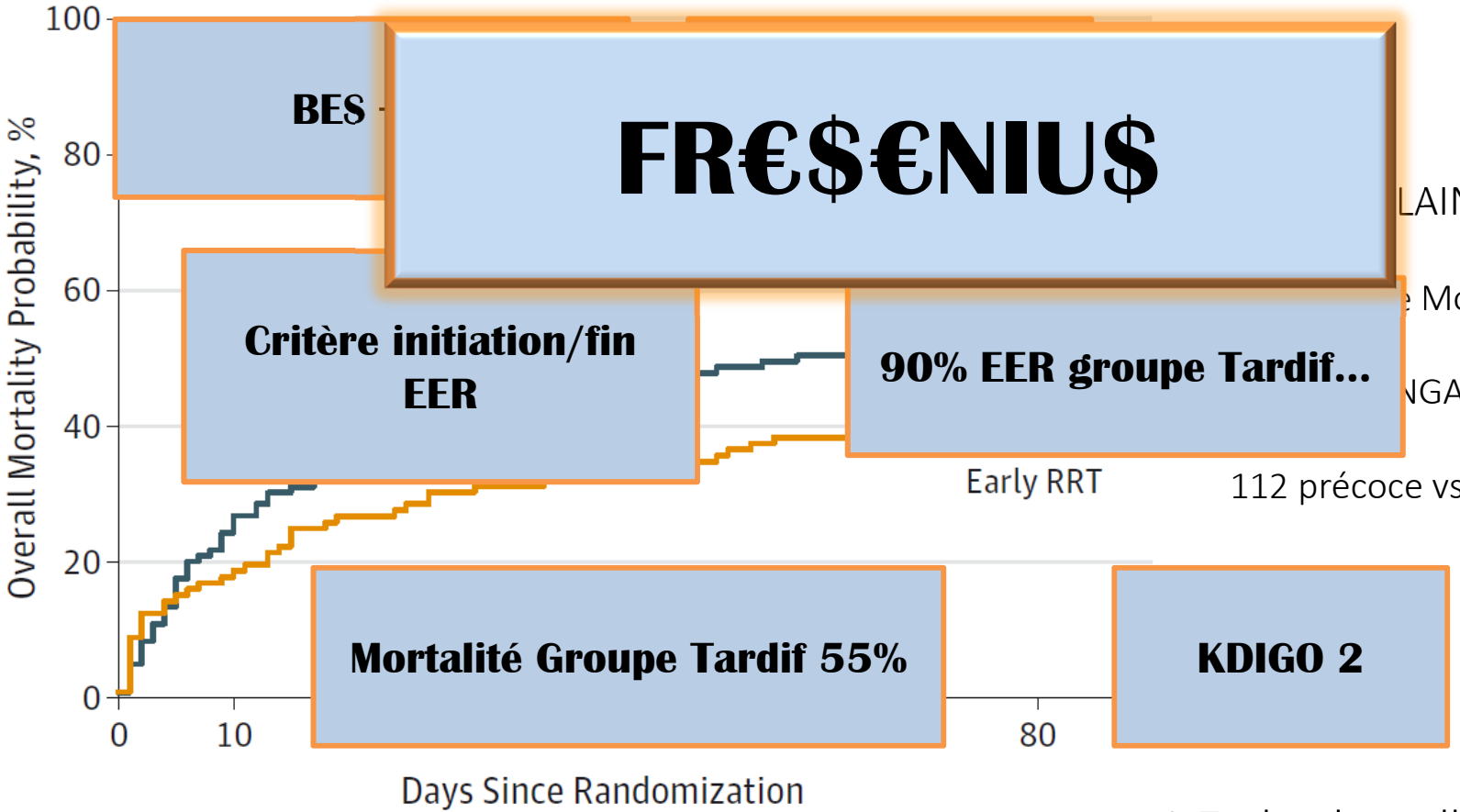
Effect of Earl… Therapy on M… With Acute K… The ELAIN Ra…

Chirurgie Cardiaque

Données CEC?

BES

FR€$€NIU$



LAIN Trial

Monocentrique

NGAL > 150ng/ml

112 précoce vs 119 tardif

Critère initiation/fin EER

90% EER groupe Tardif…

Mortalité Groupe Tardif 55%

KDIGO 2

A.Zarbock et all. JAMA 2016

Impact on mortality of the timing of renal replacement therapy in patients with severe acute kidney injury in septic shock: the IDEAL-ICU study (initiation of dialysis early versus delayed in the intensive care unit): study protocol for a randomized controlled trial

Saber Davide Barbar[1*], Christine Binquet[2], Mehran Monchi[3], Rémi Bruyère[4] and Jean-Pierre Quenot[4]

Standard versus accelerated initiation of renal replacement therapy in acute kidney injury (STARRT-AKI): study protocol for a randomized controlled trial

Orla M Smith[1,2], Ron Wald[2,3,4], Neill KJ Adhikari[5], Karen Pope[6], Matthew A Weir[7,8], Sean M Bagshaw[9*] on behalf of the Canadian Critical Care Trials Group

CONCLUSION

- Pas de différence sur le critère de jugement principal
- Urgence métabolique → EER
- Même au stade KDIGO 3 on peut se laisser du temps
- Optimisation hémodynamique
- Réévaluation précoce
- 2 essais randomisés en cours

MERCI