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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*

INTRODUCTION

- Acute kidney injury is a common condition among patients in the intensive care unit and is associated with high morbidity and mortality.

- Renal-replacement therapy is the cornerstone of the management of severe acute kidney injury.

- Many studies have focused on methods of renal-replacement therapy, but the issue of when to initiate the therapy in the absence of a potentially life-threatening complication directly related to renal failure remains a subject of debate.

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AIM OF STUDY

In the current trial they compared a strategy of early initiation of renal-replacement therapy with a strategy of delayed initiation in patients in the intensive care unit who had acute kidney injury of Kidney Disease: Improving Global Outcomes (KDIGO) classification stage 3 (serum creatinine, 3.0 times the baseline level or ≥4.0 mg per deciliter [≥354 μmol per liter]; urine output, <0.3 ml per kilogram of body weight per hour for 24 or more hours or anuria for ≥12 hours).

METHODS

Trial Design:

prospective, multicenter, open-label, two-group randomized trial conducted in 31 intensive care units in France from September 2013 through January 2016.

METHODS

- Patients:

Patients were eligible if they were adults (18 years of age or older) who were admitted to the intensive care unit with acute kidney injury that was compatible with a diagnosis of acute tubular necrosis in the context of ischemic or toxic injury and were receiving invasive mechanical ventilation, catecholamine infusion (epinephrine or norepinephrine), or both.

Patients were required to have KDIGO stage 3 acute kidney injury.

METHODS

- In the early-strategy group, renal-replacement therapy was initiated as soon as possible after randomization in order for it to be started within 6 hours after documentation of stage 3 acute kidney injury.

- In the delayed-strategy group, renal-replacement therapy was initiated if one of the laboratory abnormalities (Blood urea nitrogen of more than 112 md/dl (40 mmol/liter), Serum potassium concentration of more than 6 mmol/liter, pH below 7.15, Acute pulmonary edema due to fluid overload responsible for severe hypoxemia) developed or if oliguria or anuria lasted for more than 72 hours after randomization

METHODS

- The choice of the method of renal-replacement therapy (intermittent or continuous technique, duration and interval between sessions, device setting, and anticoagulation method) was left to the discretion of each study site and was prescribed and monitored according to national guidelines.

OUTCOMES

- The primary outcome was

Overall survival measured from the date of randomization until death or day 60.

OUTCOMES

- The secondary outcomes were

The receipt of renal-replacement therapy at least once with the delayed strategy;

The numbers of renal-replacement therapy–free days,

Dialysis catheter–free days,

Mechanical ventilation–free days,

Vasopressor therapy–free between randomization and day 28;

The Sepsis-related Organ Failure Assessment (SOFA) score at day 3 and day 7;

The length of stay in the intensive care unit and in the hospital;

The occurrence of nosocomial infections;

Complications potentially related to acute kidney injury or renal-replacement therapy

RESULTS

- 312 were assigned to the early-strategy group and 308 were assigned to the delayed-strategy group.

- One patient in the early-strategy group subsequently withdrew consent for the use of his data, leaving a total of 619 patients in the analysis

RESULTS

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

RESULTS

- The patients in the early-strategy group underwent their first renal-replacement therapy session within a median of 2 hours (interquartile range, 1 to 3) after randomization and within a median of 4.3 hours (interquartile range, 2.7 to 5.9)

- A total of 157 patients (51%) received renal-replacement therapy in the delayed-strategy group within a median of 57 hours (interquartile range, 25 to 83) after randomization (Fig. 1). The median interval between the occurrence of at least one criterion mandating renal-replacement therapy and its initiation was 4.7 hours (interquartile range, 1.7 to 10.0)

RESULTS

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)

RESULTS

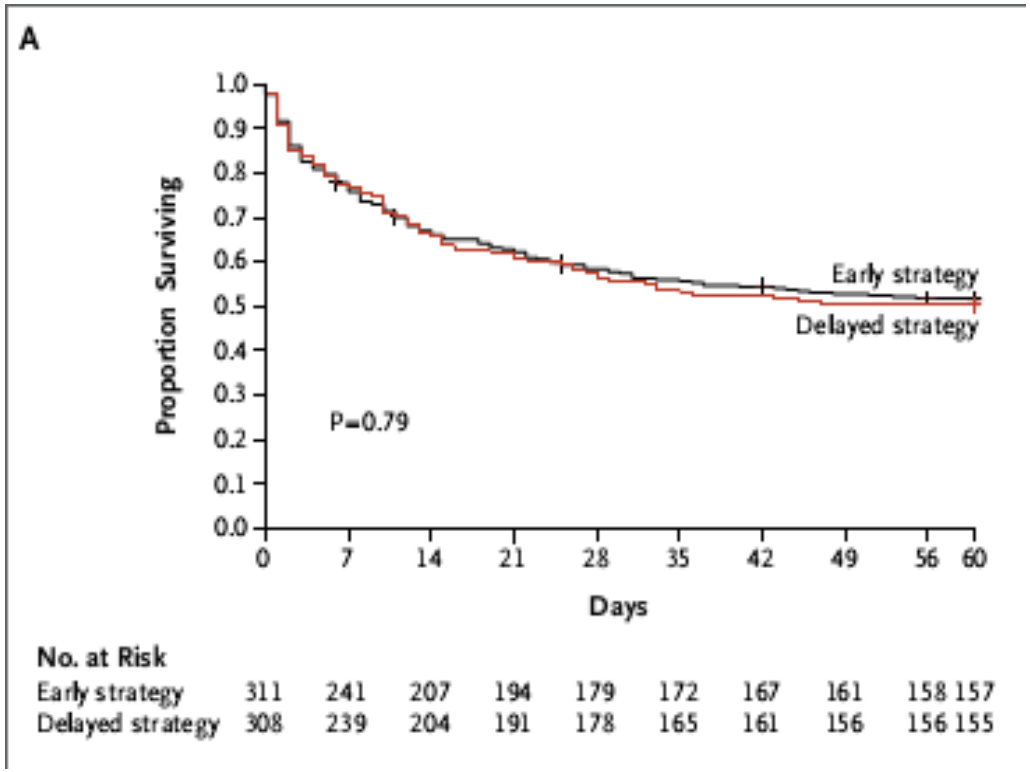
Table 2. Primary and Secondary Outcomes and Adverse Events.*

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	

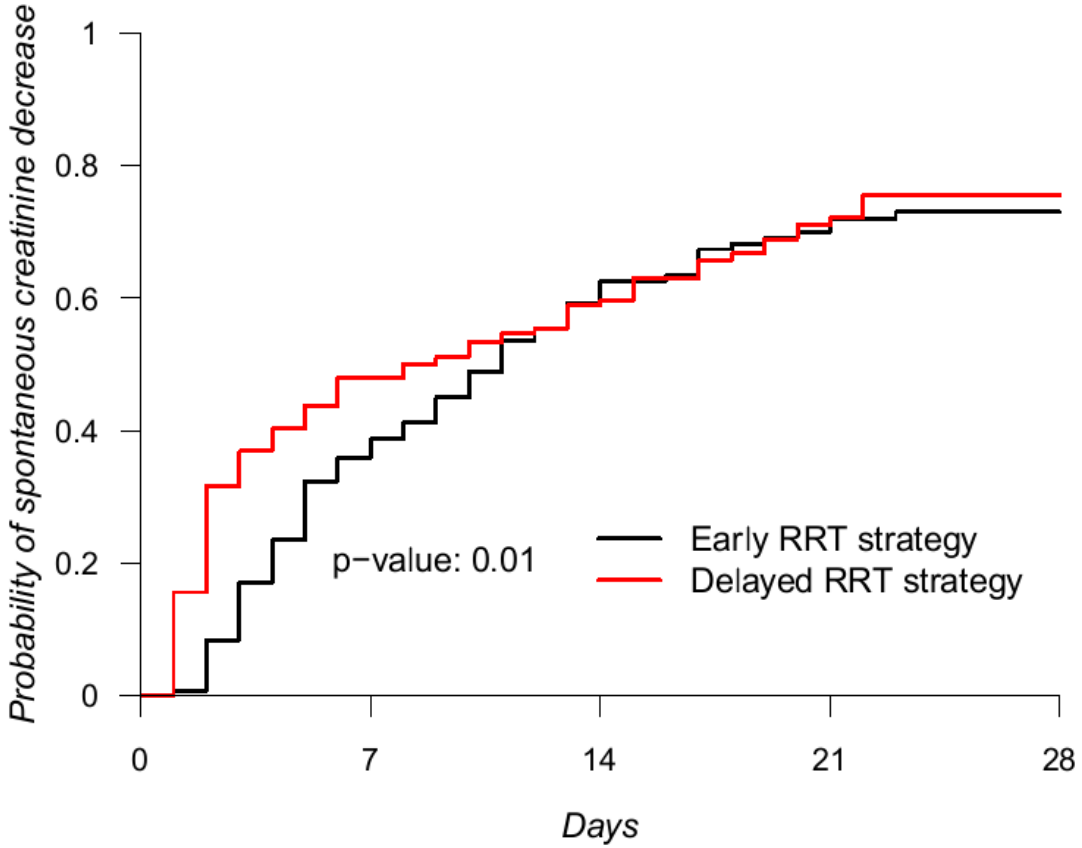
RESULTS

Complications potentially related to acute kidney injury or renal-replacement therapy — no. (%)			
Hemorrhage	27 (9)	36 (12)	0.21
Thrombocytopenia	172 (55)	165 (54)	0.70
Thrombosis	11 (4)	16 (5)	0.31
Hypokalemia	69 (22)	67 (22)	0.95
Hypophosphatemia	69 (22)	46 (15)	0.03
Hyperkalemia	16 (5)	18 (6)	0.68
Cardiac rhythm disorders — no. (%)			
Severe	29 (9)	35 (11)	0.40
Moderate	49 (16)	48 (16)	0.77
Transfusion			
Patients who received transfusion — no. (%)	146 (47)	152 (49)	0.57
Units of red cells transfused per patient	2.4±4.1	2.4±4.3	0.75
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

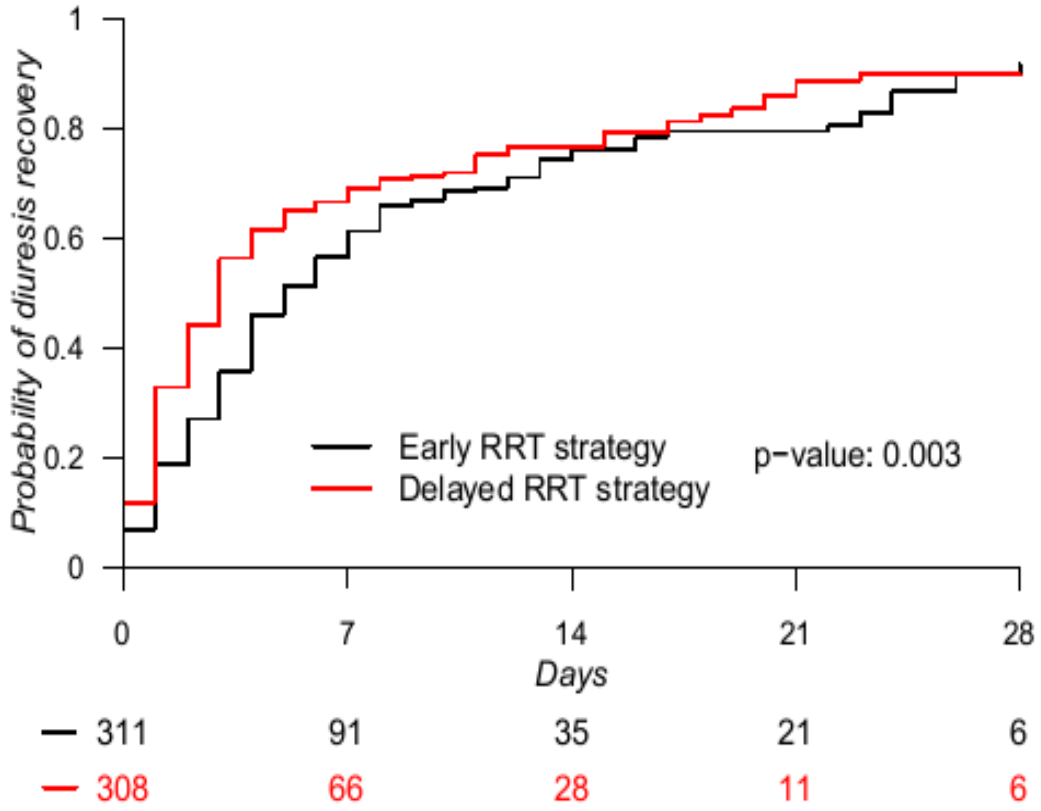
RESULTS


A
Proportion Surviving
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Early strategy
Delayed strategy
P=0.79
0
7
14
21
28
35
42
49
56
60
Days
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

RESULTS


Probability of spontaneous creatinine decrease
1
0.8
0.6
0.4
0.2
0
p−value: 0.01
Early RRT strategy
Delayed RRT strategy
0
7
14
21
28
Days
No. at Risk
311 136 60 32 14
308 105 51 26 16

RESULTS


Probability of diuresis recovery
1
0.8
0.6
0.4
0.2
0
Early RRT strategy
Delayed RRT strategy
p−value: 0.003
0
7
14
21
28
Days
311
91
35
21
6
308
66
28
11
6

RESULTS

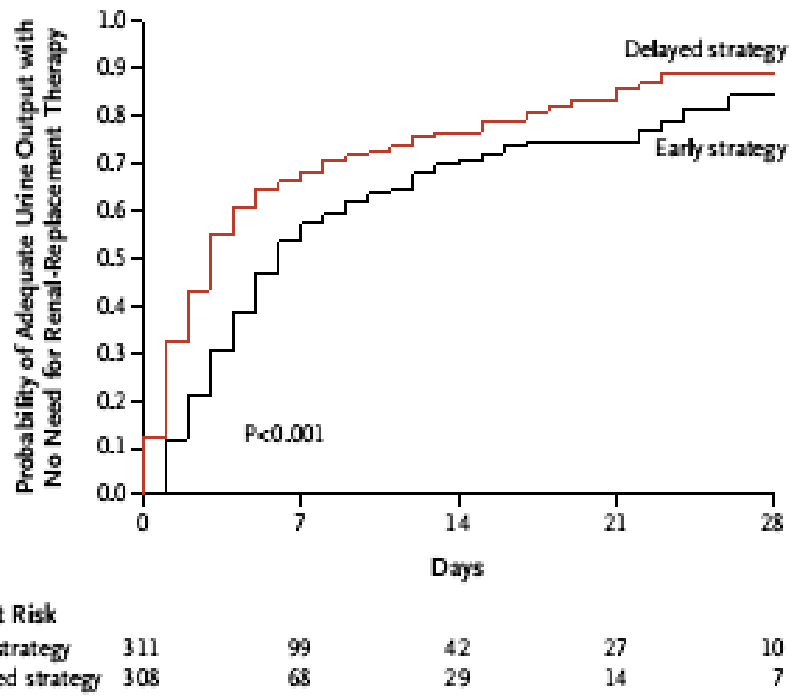


Figure 2. Probability of Adequate Urine Output without the Need for Renal-Replacement Therapy.

Shown are the Kaplan–Meier curves of the probability of a patient having urine output, for at least 1 day, of more than 1000 ml per 24 hours in the absence of diuretic treatment or more than 2000 ml per 24 hours with diuretic treatment and not requiring initiation or resumption of renal-replacement therapy for at least 7 days, from randomization to day 28 (see also Fig. S3 in the Supplementary Appendix).

RESULTS

- A post hoc exploratory analysis was performed to compare patients who never received renal-replacement therapy with those who received it either early or late. The lowest mortality at day 60 (37.1%) was found among patients who never received renal-replacement therapy, and the highest mortality (61.8%) was found among patients who received therapy late, whereas intermediate mortality (48.5%) was found among patients who received therapy early ($P<0.001$).

CONCLUSION

Trial involving critically ill patients with severe acute kidney injury showed no significant difference in mortality with a strategy of delayed initiation as compared with early initiation of renal-replacement therapy.