ORIGINAL ARTICLE

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

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## ABSTRACT

### BACKGROUND

The timing of renal-replacement therapy in critically ill patients who have acute kidney injury but no potentially life-threatening complication directly related to renal failure is a subject of debate.

### METHODS

In this multicenter randomized trial, we assigned patients with severe acute kidney injury (Kidney Disease: Improving Global Outcomes [KDIGO] classification, stage 3 [stages range from 1 to 3, with higher stages indicating more severe kidney injury]) who required mechanical ventilation, catecholamine infusion, or both and did not have a potentially life-threatening complication directly related to renal failure to either an early or a delayed strategy of renal-replacement therapy. With the early strategy, renal-replacement therapy was started immediately after randomization. With the delayed strategy, renal-replacement therapy was initiated if at least one of the following criteria was met: severe hyperkalemia, metabolic acidosis, pulmonary edema, blood urea nitrogen level higher than 112 mg per deciliter, or oliguria for more than 72 hours after randomization. The primary outcome was overall survival at day 60.

### RESULTS

A total of 620 patients underwent randomization. The Kaplan–Meier estimates of mortality at day 60 did not differ significantly between the early and delayed strategies; 150 deaths occurred among 311 patients in the early-strategy group (48.5%; 95% confidence interval [CI], 42.6 to 53.8), and 153 deaths occurred among 308 patients in the delayed-strategy group (49.7%, 95% CI, 43.8 to 55.0; P=0.79). A total of 151 patients (49%) in the delayed-strategy group did not receive renal-replacement therapy. The rate of catheter-related bloodstream infections was higher in the early-strategy group than in the delayed-strategy group (10% vs. 5%, P=0.03). Diuresis, a marker of improved kidney function, occurred earlier in the delayed-strategy group (P<0.001).

### CONCLUSIONS

In a trial involving critically ill patients with severe acute kidney injury, we found no significant difference with regard to mortality between an early and a delayed strategy for the initiation of renal-replacement therapy. A delayed strategy averted the need for renal-replacement therapy in an appreciable number of patients. (Funded by the French Ministry of Health; ClinicalTrials.gov number, NCT01932190.)

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Acute kidney injury is a common condition among patients in the intensive care unit[1-4] and is associated with high morbidity and mortality.[2,5-8] Renal-replacement therapy is the cornerstone of the management of severe acute kidney injury. Many studies have focused on methods of renal-replacement therapy,[5,6,8,9] 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. Indirect evidence has suggested that early renal-replacement therapy could confer a survival benefit.[10-12] However, two observational studies reported high survival rates among patients who did not receive renal-replacement therapy,[13,14] and one study reported adverse outcomes in association with very early renal-replacement therapy in patients with sepsis.[15] Early initiation of renal-replacement therapy may allow for better control of fluid and electrolyte status, removal of uremic toxins, and prevention of complications such as gastric hemorrhage and metabolic encephalopathy.[16] Delaying renal-replacement therapy initiation is intuitively unlikely to have any immediate benefit per se. However, a delay may allow time for the stabilization of a patient's condition before renal-replacement therapy is initiated and may avoid the need for such support, which is not devoid of risk.[17]

Given such uncertainties, there is heterogeneity among criteria for the initiation of renal-replacement therapy.[18,19] Indeed, several authorities consider an appropriate multicenter, randomized, controlled trial involving patients with acute kidney injury to be an important research priority.[20,21] To fill this perceived need, in the current trial we 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).[22]

## METHODS

### TRIAL DESIGN AND OVERSIGHT

The Artificial Kidney Initiation in Kidney Injury (AKIKI) trial was an institutionally sponsored, unblinded, prospective, multicenter, open-label, two-group randomized trial conducted in 31 intensive care units in France from September 2013 through January 2016. The protocol (which has been published previously[23]) was approved by the ethics committee of the French Society of Intensive Care Medicine and by the appropriate French legal authority (Comité de Protection des Personnes d'Ile de France VI) for all participating centers and is available with the full text of this article at NEJM.org. The Direction de la Recherche Clinique de l'Assistance Publique-Hôpitaux de Paris, French Ministry of Health, supervised the use of the study funding.

The investigators informed patients or their surrogates about the trial both orally and with a written document. In accordance with French law, written informed consent was not required, because the standard of care encompasses both study interventions. Patients or their surrogates were informed that they could decline to participate at any time, and their decision was recorded in patient files (see the Supplementary Appendix, available at NEJM.org).

The trial was overseen by a steering committee that presented information regarding the rate of inclusion of new patients to the investigators by e-mail every 3 months and during meetings in January 2014 and January 2015. Two planned interim analyses were performed by an independent data and safety monitoring board, the members of which were unaware of the study-group assignments. An investigator at each center was responsible for enrolling patients, ensuring adherence to the protocol, and completing the electronic case-report form. The first author vouches for the accuracy and the completeness of the reported data and for the adherence of the trial to the protocol. All analyses were performed by the study statistician (the second author) in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines.

### 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. To undergo randomiza-

tion, patients were required to have KDIGO stage 3 acute kidney injury (see the Supplementary Appendix).[22] The main exclusion criteria at the time of enrollment were the following severe laboratory abnormalities: a blood urea nitrogen level higher than 112 mg per deciliter (40 mmol per liter), a serum potassium concentration greater than 6 mmol per liter (or greater than 5.5 mmol per liter despite medical treatment), a pH below 7.15 in the context of either pure metabolic acidosis (partial pressure of arterial carbon dioxide [$Paco_2$] below 35 mm Hg) or mixed acidosis ($Paco_2$ of 50 mm Hg or more without the possibility of increasing alveolar ventilation), and acute pulmonary edema due to fluid overload responsible for severe hypoxemia requiring an oxygen flow rate greater than 5 liters per minute to maintain a peripheral capillary oxygen saturation ($Spo_2$) greater than 95% or requiring a fraction of inspired oxygen ($Fio_2$) greater than 50% in patients receiving mechanical ventilation and despite diuretic therapy. These criteria were later used to establish the indication for renal-replacement therapy in patients assigned to the delayed strategy (i.e., therapy was initiated in that group if any of these laboratory abnormalities developed after enrollment). Other exclusion criteria are detailed in the Supplementary Appendix.

### RANDOMIZATION

The randomization list was computer-generated, balanced by blocks of variable and undisclosed size, and stratified according to center. Patients underwent randomization within 5 hours after validation of stage 3 acute kidney injury (which left 1 hour to initiate renal-replacement therapy in patients who were assigned to the early strategy); patients were randomly assigned in a 1:1 ratio to either early initiation of renal-replacement therapy (early-strategy group) or delayed initiation of renal-replacement therapy (delayed-strategy group). Concealment of the study-group assignments was achieved with the use of a centralized, secure, interactive, Web-based response system (CleanWeb, Telemedicine Technologies) that was accessible from each study center.

### INTERVENTIONS

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 defined above developed or if oliguria or anuria lasted for more than 72 hours after randomization (Table S1 in the Supplementary Appendix). 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.[24] All centers had extensive experience in both the management of acute kidney injury and techniques of renal-replacement therapy.

In both groups, discontinuation of renal-replacement therapy was considered if the spontaneous urine output was 500 ml or higher per 24 hours and was highly recommended if the spontaneous urine output was higher than 1000 ml per 24 hours in the absence of diuretic therapy or if urine output was higher than 2000 ml per 24 hours in patients who were receiving diuretic therapy. Discontinuation of renal-replacement therapy was mandatory if diuresis was sufficient to allow for spontaneous decrease in serum creatinine concentration. Renal-replacement therapy was resumed if diuresis appeared to be insufficient to result in a spontaneous decrease in creatinine level or if urine output fell below 1000 ml per 24 hours in the absence of diuretic therapy (or below 2000 ml per 24 hours in patients receiving diuretic therapy).

### OUTCOMES

The duration of follow-up for each patient was 60 days from randomization. The primary outcome was overall survival measured from the date of randomization until death or day 60. For patients who were discharged alive from the intensive care unit, information on the primary outcome was obtained either directly from the patient or the patient's relatives or from the physician who was in charge when the patient was still hospitalized. Data from patients who were alive at day 60 were censored, and data from patients who were lost to follow-up before day 60 were censored at their last follow-up assessment.

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, and vasopressor therapy–free days (i.e., days alive and

without the intervention; a value of 0 days was assigned for patients who died) between randomization and day 28; the Sepsis-related Organ Failure Assessment (SOFA) score[25] at day 3 and day 7; the vital status at day 28; the length of stay in the intensive care unit and in the hospital; the proportion of patients with treatment limitations (i.e., withholding or withdrawal of treatment); the occurrence of nosocomial infections; and complications potentially related to acute kidney injury or renal-replacement therapy (see the Supplementary Appendix).

Other prespecified outcomes included the time between randomization and the initiation of renal-replacement therapy, the time between the occurrence of at least one of the criteria that mandated renal-replacement therapy in the delayed-strategy group and actual initiation of therapy, the number of sessions of renal-replacement therapy, and dependence on renal-replacement therapy at days 28 and 60. Because diuresis was closely monitored, we also noted the number of patients who, for at least 1 day, had urine output of more than 1000 ml per 24 hours in the absence of diuretic therapy or of more than 2000 ml per 24 hours with diuretic therapy and who did not require initiation or resumption of renal-replacement therapy for at least 7 days. The total numbers of units of red cells transfused was also compared. These outcomes had not been prespecified in the protocol when the trial was being designed.

### STATISTICAL ANALYSIS

This trial was designed as a sequential study (with two interim analyses)[26] (see the Supplementary Appendix). On the basis of published data, death at day 60 was expected in 55%[6,7,9,27] of patients requiring renal-replacement therapy in the intensive care unit. At the time that the trial was being designed, indirect evidence[13,14,28] suggested that mortality might be expected to be 15 percentage points lower in association with delayed renal-replacement therapy. We calculated that with a total sample size of 546 patients, the study would have 90% power to show a 15-percentage-point lower mortality with the delayed strategy than with the early strategy (corresponding to a relative risk of 0.65 in favor of the delayed strategy, under an assumption of an exponential distribution of survival times), at a two-sided alpha level of 5%. Two interim efficacy analyses were planned, after the observation of 90 and 180 deaths. To maintain an overall type I error rate of 5%, the significance level of each analysis was adjusted with the use of the O'Brien and Fleming approach.[29] To maintain a power of 90%, this approach also necessitated an increase in the planned number of patients, to 560. To take into account a potential loss to follow-up of 10%, enrollment of 620 patients was planned.

Baseline characteristics in each study group were analyzed as frequencies and percentages for categorical variables and as means and standard deviations or medians and interquartile ranges for continuous variables, as appropriate. The overall survival (primary outcome), estimated by the Kaplan–Meier method, was analyzed in the intention-to-treat population and compared between the two groups with the use of a log-rank test. Further stratification according to center, adjustment for baseline prognostic factors (Simplified Acute Physiology Score [SAPS] III, treatment or no treatment with vasopressors, receipt or no receipt of mechanical ventilation, presence or absence of septic shock, and time between admission to the intensive care unit and development of acute kidney injury of <7 days vs. ≥7 days), and determination of baseline predictors of renal-replacement therapy in the delayed-strategy group were also performed with a Cox semiparametric proportional-hazards model.

Categorical variables were compared with the use of the chi-square test or Fisher's exact test, and continuous variables were compared with the use of Student's t-test or Wilcoxon test, as appropriate. The time to recovery of renal function, as marked by diuresis, was described by means of the Kaplan–Meier method and compared with a log-rank test. For this analysis, data from all patients were censored at the time of death or at day 28.

With the exception of the primary outcome (for which the type I error rate was adapted for interim analyses), all analyses were performed at a two-sided alpha level of 5%. All analyses were performed with R software, version 3.2.3 (R Foundation for Statistical Computing).

## RESULTS

### PATIENTS

A total of 5528 patients were eligible for inclusion in the trial, and 620 patients underwent randomization (Fig. S1 in the Supplementary Appendix); 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.

The characteristics of the patients were well balanced between the two study groups, with the exception of the prothrombin ratio (i.e., the ratio of a patient's prothrombin time to that in a control sample, expressed as a percentage), which was significantly lower in the delayed-strategy group (Table 1, and Table S2 in the

**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 |

* Plus–minus values are means ±SD. A total of 620 patients underwent randomization, and 1 patient subsequently withdrew permission for the use of his data. To convert values for creatinine to micromoles per liter, multiply by 88.4. To convert values for blood urea nitrogen to millimoles per liter, multiply by 0.357. Additional data on baseline characteristics are provided in Table S2 in the Supplementary Appendix. ARDS denotes acute respiratory distress syndrome, and ICU intensive care unit.

† The serum creatinine concentration before ICU admission was either determined with the use of values measured in the 12 months preceding the ICU stay or was estimated.[22]

‡ The Simplified Acute Physiology Score (SAPS) III ranges from 0 to 146, with higher scores indicating more severe disease and a higher risk of death.

§ The Sepsis-related Organ Failure Assessment (SOFA) score ranges from 0 to 24, with higher scores indicating more severe organ failure.[25]

¶ Some patients were exposed to more than one nephrotoxic agent.

‖ Sepsis was defined as suspected or confirmed infection, with at least two of four signs of a systemic inflammatory response. Severe sepsis was defined as sepsis with evidence of organ dysfunction. Septic shock was defined as sepsis-induced hypotension despite fluid resuscitation of at least 30 ml per kilogram of body weight of intravenous fluid administered within the period spanning the 4 hours before and 4 hours after initiation of vasopressor therapy.

Supplementary Appendix). Sepsis was present in 494 patients (80%), and 389 patients (63%) had been exposed to nephrotoxic agents.

### RENAL-REPLACEMENT THERAPY

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) after documentation of stage 3 acute kidney injury and of the fulfillment of other inclusion criteria. In this group, six patients did not receive renal-replacement therapy (see the Supplementary Appendix).

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). Five patients received renal-replacement therapy without meeting the initiation criteria. Persistence of oliguria or anuria for more than 72 hours after randomization and a blood urea nitrogen level higher than 112 mg per deciliter (40 mmol per liter) were the two most common reasons for renal-replacement therapy (Table S3 in the Supplementary Appendix).

Patient characteristics at the time of initiation of renal-replacement therapy are provided in Table S4 in the Supplementary Appendix. Metabolic abnormalities were more marked in the delayed-strategy group than in the early-strategy group. Details regarding the methods used for renal-replacement therapy, the changes in blood urea nitrogen and serum creatinine levels during follow-up, and the baseline predictors of renal-replacement therapy in the delayed-strategy group are provided in the Supplementary Appendix.

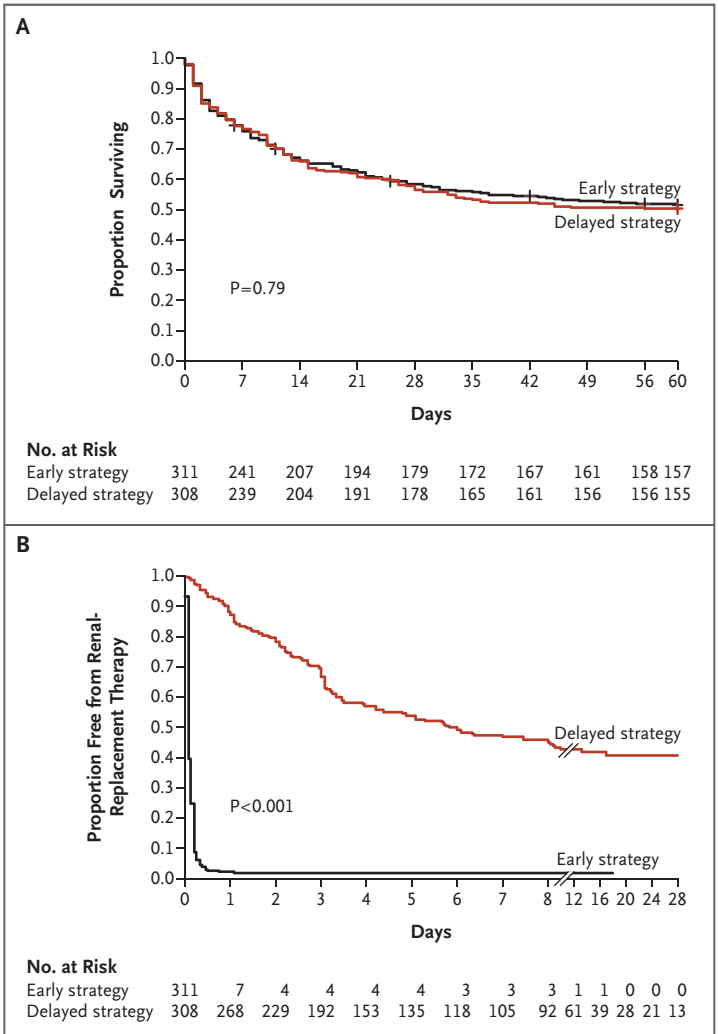


**Figure 1. Probability of Survival and Timing of Renal-Replacement Therapy.**

Panel A shows Kaplan–Meier curves of the probability of survival from randomization to day 60. Panel B shows the time from randomization to the initiation of renal-replacement therapy, stratified according to study group. Some patients in the early-strategy group received renal-replacement therapy after 6 hours because of other emergencies resulting in postponement of the initiation of therapy by the medical team, a lack of availability of the renal-replacement therapy machine, or difficulties with catheter insertion. Other reasons for delay included situations such as a surgical procedure or radiologic examinations that needed to be performed before the initiation of renal-replacement therapy.

### PRIMARY AND SECONDARY OUTCOMES

Follow-up data at 60 days were available for 614 patients (99%); a total of 303 deaths had been observed by day 60 (150 in the early-strategy group and 153 in the delayed-strategy group). The mortality rates in our analysis were estimated with the use of the Kaplan–Meier method. The Kaplan–Meier estimate of the overall mortality at day 60 was 49.1% (95% confidence interval [CI], 45.0 to 52.9). Mortality did not differ significantly between the two study groups: 48.5% (95% CI, 42.6 to 53.8) in the early-strategy group and 49.7% (95% CI, 43.8 to 55.0) in the delayed-strategy group (P=0.79) (Fig. 1). Further stratification according to center and adjustment for important prognostic factors did not materially change the results.

A post hoc exploratory analysis was performed to compare patients who never received renal-

**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 |
| 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 |

* Plus–minus values are means ±SD. The numbers of days free from renal-replacement therapy, mechanical ventilation, and vasopressor therapy was defined as the number of days alive without the intervention at day 28; for patients who died, a value of 0 days was assigned. IQR denotes interquartile range.
† Mortality rates were estimated with the use of the Kaplan–Meier method. The vital status at day 60 was not available for 7 patients (see the Supplementary Appendix).
‡ This analysis was stratified according to center and adjusted for the following baseline characteristics: receipt or no receipt of mechanical ventilation, SAPS III, presence or absence of septic shock, treatment or no treatment with vasopressors, and time between admission and acute kidney injury.
§ Treatment limitations (withholding or withdrawal of treatment) could involve any treatment used during the ICU stay.
¶ Catheter-related bloodstream infections were defined according to the 2009 guidelines from the Infectious Diseases Society of America.[30]
‖ Definitions are provided in the Supplementary Appendix.

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). Patients who never received renal-replacement therapy were less ill at baseline, and patients who received it late were the most severely ill patients at baseline. The differences in mortality became nonsignificant after adjustment for baseline severity of illness, which suggests that these observed differences were markedly confounded (see the Supplementary Appendix).

In the delayed-strategy group, 95 patients (61%) of the 155 who were alive at day 60 had not received renal-replacement therapy, and the total number of therapy sessions differed substantially between the study groups (Table S5 in the Supplementary Appendix). Mortality at day 28, numbers of mechanical ventilation–free and vasopressor-free days, length of stay in intensive care unit and in the hospital, and dependence on renal-replacement therapy at day 28 and 60 did not differ significantly between the two study groups (Table 2). However, the number of days free from renal-replacement therapy was significantly higher, and the rate of catheter-related bloodstream infections was significantly lower, in the delayed-strategy group than in the early-strategy group (Table 2).

The rate of complications that were potentially related to acute kidney injury or renal-replacement therapy did not differ significantly between the two study groups, with the exception of hypophosphatemia, which was more common in the early-strategy group (Table 2). The overall rate of hemorrhage did not differ significantly between the study groups (Table 2). Whereas there was no significant difference between the groups in the rate of either dialysis catheter–related or digestive-tract blood loss, blood loss from other causes was significantly more common in the delayed-strategy group (Table S8 in the Supplementary Appendix). The numbers of patients who received red cells and the amount of red cells received per patient did not differ significantly between the groups (Table 2). Adequate diuresis together with no need for renal-replacement therapy were observed earlier in the delayed-strategy group than in the early-strategy group (P<0.001) (Fig. 2).

## DISCUSSION

In this trial, a strategy of delayed initiation of renal-replacement therapy in critically ill patients with severe acute kidney injury obviated the need for renal-replacement therapy in almost 50% of cases (resulting in a considerable difference in the total number of renal-replacement therapy sessions). Mortality at day 60 did not differ significantly between the early-strategy group and the delayed-strategy group.

The available knowledge about the initiation of renal-replacement therapy during acute kidney injury derives predominantly from observational studies.[31-33] Meta-analyses have suggested that a survival advantage is associated with early renal-replacement therapy.[34,35] A major pitfall of such observational studies is that all patients received renal-replacement therapy — that is, there was no control group, and the possibility that delaying renal-replacement therapy might provide time for spontaneous renal recovery was not explored. Two small, single-center, randomized, controlled trials have addressed this issue,[27,36] but they showed no difference in mortality. The current results address the timing of renal-replacement therapy.[23] Two other large multicenter studies are in progress,[37,38] and we speculate that the results of those studies will confirm our findings, particularly because a pilot study showed that a delayed strategy averted the need for renal-replacement therapy in an appreciable number of patients.[39]

The 50% mortality among patients in our trial was close to our working hypothesis and consonant with the rate in other studies.[5,7-9] Patients in the current study received renal-replacement therapy at a median of 2 hours after randomization with the early strategy and at a median of 57 hours with the delayed strategy. Contrary to our hypothesis, no survival benefit was observed with the delayed strategy of renal-replacement therapy.

Although the survival curves were similar in the two groups, the recovery of renal function, as marked by diuresis, was more rapid and catheter-related infections occurred less frequently in the delayed-strategy group than in the early-strategy group. Subtle or undetected circulatory

alterations might have slowed the apparent recovery of renal function in the early-strategy group. The rate of gastrointestinal bleeding did not differ significantly between the groups. Finally, the lengths of stay in the intensive care unit and in the hospital were similar in the two groups, which indicates that allowing time for renal function recovery did not lead to prolongation of the stay in the intensive care unit.

Our findings may not be generalizable, because more than 50% of the patients in our trial received intermittent hemodialysis as the first method of therapy and only 30% of the patients received continuous renal-replacement therapy as the sole method (with no intermittent dialysis at any time). Although a previously published large, randomized, controlled trial did not show differences in mortality according to the method of renal-replacement therapy,[9] some investigators have voiced concern about the potentially deleterious effects of intermittent hemodialysis in patients whose condition is unstable.[40]

Our trial has potential limitations. First, the power of our study to distinguish a significant difference in mortality could be questioned. However, to detect an effect size of 1.2 percentage points (i.e., the difference in mortality that we found between the two groups in our study) with a power of 90%, a sample of more than 70,000 patients would be required. Second, although we did not use Kt/V (a measure of the clearance of urea in which K represents the rate of urea clearance by the dialyzer, t is the duration of dialysis, and V is the volume of distribution of urea in the patient) to evaluate the dose of renal-replacement therapy, low urea levels in serum were maintained during therapy. Third, the patients in the trial population had advanced acute kidney injury, and therefore our results may not be generalizable to patients with different KDIGO stages of acute kidney injury. Finally, some could interpret the finding of higher mortality among patients who received late renal-replacement therapy as a deleterious effect of this strategy. However, the patients who received late renal-replacement therapy obviously had more severe illness than those who did not, and further adjustment according to baseline severity suggests that this observed crude difference was confounded (see the Supplementary Appendix).

Our study should not be interpreted as suggesting that a "wait and see" approach is safe for all patients. Indeed, careful surveillance is mandatory when deciding to delay renal-replacement therapy in patients with severe acute kidney injury so that any complication will be detected and renal-replacement therapy initiated without delay. In our trial, delaying the initiation of therapy allowed many patients to recover from acute kidney injury without embarking on such a treatment course.

In conclusion, our 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.

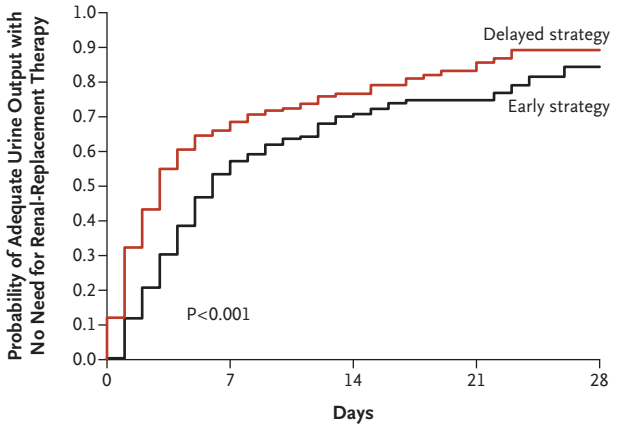


**Figure 2. Probability of Adequate Urine Output without the Need for Renal-Replacement Therapy.**

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).

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## APPENDIX

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