ORIGINAL ARTICLE

Timing of Renal-Replacement Therapy in Patients with Acute Kidney Injury and Sepsis

S.D. Barbar, R. Clere-Jehl, A. Bourredjem, R. Hernu, F. Montini, R. Bruyère, C. Lebert, J. Bohé, J. Badie, J.-P. Eraldi, J.-P. Rigaud, B. Levy, S. Siami, G. Louis, L. Bouadma, J.-M. Constantin, E. Mercier, K. Klouche, D. du Cheyron, G. Piton, D. Annane, S. Jaber, T. van der Linden, G. Blasco, J.-P. Mira, C. Schwebel, L. Chimot, P. Guiot, M.-A. Nay, F. Meziani, J. Helms, C. Roger, B. Louart, R. Trusson, A. Dargent, C. Binquet, and J.-P. Quenot, for the IDEAL-ICU Trial Investigators and the CRICS TRIGGERSEP Network*

ABSTRACT

BACKGROUND

Acute kidney injury is the most frequent complication in patients with septic shock and is an independent risk factor for death. Although renal-replacement therapy is the standard of care for severe acute kidney injury, the ideal time for initiation remains controversial.

METHODS

In a multicenter, randomized, controlled trial, we assigned patients with early-stage septic shock who had severe acute kidney injury at the failure stage of the risk, injury, failure, loss, and end-stage kidney disease (RIFLE) classification system but without life-threatening complications related to acute kidney injury to receive renal-replacement therapy either within 12 hours after documentation of failure-stage acute kidney injury (early strategy) or after a delay of 48 hours if renal recovery had not occurred (delayed strategy). The failure stage of the RIFLE classification system is characterized by a serum creatinine level 3 times the baseline level (or ≥4 mg per deciliter with a rapid increase of ≥0.5 mg per deciliter), urine output less than 0.3 ml per kilogram of body weight per hour for 24 hours or longer, or anuria for at least 12 hours. The primary outcome was death at 90 days.

RESULTS

The trial was stopped early for futility after the second planned interim analysis. A total of 488 patients underwent randomization; there were no significant between-group differences in the characteristics at baseline. Among the 477 patients for whom follow-up data at 90 days were available, 58% of the patients in the early-strategy group (138 of 239 patients) and 54% in the delayed-strategy group (128 of 238 patients) had died (P=0.38). In the delayed-strategy group, 38% (93 patients) did not receive renal-replacement therapy. Criteria for emergency renal-replacement therapy were met in 17% of the patients in the delayed-strategy group (41 patients).

CONCLUSIONS

Among patients with septic shock who had severe acute kidney injury, there was no significant difference in overall mortality at 90 days between patients who were assigned to an early strategy for the initiation of renal-replacement therapy and those who were assigned to a delayed strategy. (Funded by the French Ministry of Health; IDEAL-ICU ClinicalTrials.gov number, NCT01682590.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Quenot at the Critical Care Department, University Hospital François Mitterand, 14 rue Paul Gaffarel, 21079 Dijon, France.

*A complete list of the IDEAL-ICU Trial Investigators is provided in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2018;379:1431-42.
DOI: 10.1056/NEJMoa1803213

A Quick Take is available at NEJM.org

Acute kidney injury is a frequent complication in patients hospitalized in the intensive care unit (ICU) for septic shock[1-3] and is associated with high mortality.[3-7] Acute kidney injury associated with sepsis is characterized by a distinct pathophysiology,[8] and patients with acute kidney injury and septic shock may have a different response to renal-replacement therapy than patients with acute kidney injury without septic shock.[9] In managing severe acute kidney injury, whether to provide renal-replacement therapy and, if so, when to initiate it are unclear. It is widely accepted that if there are life-threatening complications of acute kidney injury, such as hyperkalemia or metabolic acidosis, renal-replacement therapy should be initiated immediately. However, in the absence of such complications, the appropriate timing of the initiation of renal-replacement therapy remains unclear. Some clinical investigators have explored strategies of very early renal-replacement therapy to treat the initial phase of septic shock, but in reports of such efforts, hemofiltration techniques were introduced, irrespective of the presence of renal failure.[10,11] Recently, two randomized, controlled trials comparing an early strategy with a delayed strategy for the initiation of renal-replacement therapy reported conflicting results.[12,13] Thus, whether there is a benefit to early initiation of renal-replacement therapy is not established, and the magnitude of the risk (if any risk exists) associated with delaying the initiation of renal-replacement therapy in the setting of acute kidney injury associated with sepsis is not known. Here we report the results of a randomized, multicenter, controlled trial that we performed to investigate the effect on 90-day mortality of the timing of the initiation of renal-replacement therapy in patients with septic shock and severe acute kidney injury.

METHODS

TRIAL DESIGN

The Initiation of Dialysis Early Versus Delayed in the Intensive Care Unit (IDEAL-ICU) trial was a randomized, controlled, open-label, multicenter trial that was designed to compare an early strategy with a delayed strategy for the initiation of renal-replacement therapy in the management of severe acute kidney injury in patients in the initial phase of septic shock. (Trial definitions are provided in Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.) The trial design has been reported previously; the protocol is available at NEJM.org.[14] With the early strategy, renal-replacement therapy was started within 12 hours after the onset of acute kidney injury that was determined to be at the failure stage of the risk, injury, failure, loss, and end-stage kidney disease (RIFLE) classification (see the Box in the Supplementary Appendix).[15] With the delayed strategy, renal-replacement therapy was initiated after a delay of 48 hours if renal function did not spontaneously recover and if no condition meeting the criteria for emergency renal-replacement therapy developed.

TRIAL OVERSIGHT

The University Hospital of Dijon, France, supervised the use of the trial funding. An independent data and safety monitoring board reviewed safety data and results at two planned interim analyses. This trial received approval for all participating centers from the Dijon ethics committee (Comité de Protection des Personnes Est I). The trial was overseen by a trial management committee. The first author wrote the first draft of the manuscript, which was reviewed by the management committee. Statistical analyses were performed by the trial statistician in accordance with International Conference on Harmonisation Good Clinical Practice guidelines. The authors vouch for the accuracy and completeness of the reported analyses and for the fidelity of the trial to the protocol. There was no commercial support for the trial. Further details are provided in the Supplementary Appendix.

TRIAL POPULATION

Patients were eligible if they were 18 years of age or older, were admitted to the ICU in the early phase of septic shock (within 48 hours after the start of vasopressor therapy), and had acute kidney injury meeting at least one of the following criteria for the failure stage of the RIFLE classification: oliguria (urine output <0.3 ml per kilogram of body weight per hour for ≥24 hours), anuria for 12 hours or more, or a serum creatinine level 3 times the baseline level (or ≥4 mg per deciliter [≥350 μmol per liter] accompanied by a

rapid increase of ≥0.5 mg per deciliter [≥44 μmol per liter]). Written informed consent was obtained from the patient or a responsible surrogate either before randomization or as soon as possible thereafter (see the Informed Consent Procedures section in the Supplementary Appendix). Patients requiring emergency renal-replacement therapy before randomization were not eligible for the trial. A detailed list of inclusion and exclusion criteria is provided in Table S2 in the Supplementary Appendix.

RANDOMIZATION

Randomization was performed by means of an online response system, with the use of Tenalea software (FormsVision BV), during the first 48 hours of septic shock after acute kidney injury was determined to be at the failure stage of the RIFLE classification. Randomization was performed on the basis of a minimization technique with stratification according to center, age, Sepsis-related Organ Failure Assessment (SOFA) score (which ranges from 0 to 24, with higher scores indicating more severe organ failure),[16] site, and type of infection. Patients were randomly assigned to the early-strategy group or the delayed-strategy group in a 1:1 ratio. The INSERM Clinical Epidemiology Unit (Centre d'Investigation Clinique 1432 in Dijon, France) managed the data and generated blinded reports for the data and safety monitoring board.

INTERVENTIONS

In the early-strategy group, renal-replacement therapy was initiated within 12 hours after documentation of failure-stage acute kidney injury. Patients assigned to the delayed-strategy group were closely monitored after randomization to detect the development of any one of the following conditions included in the criteria for emergency renal-replacement therapy: hyperkalemia (potassium level >6.5 mmol per liter), metabolic acidosis (pH <7.15), or fluid overload (extravascular fluid overload that was refractory to diuretics, with pulmonary edema). If any of these conditions occurred, renal-replacement therapy was initiated as soon as possible. If none of these conditions occurred, renal-replacement therapy was initiated in this group 48 hours after the diagnosis of acute kidney injury. Renal-replacement therapy was not initiated in the delayed-strategy group if spontaneous renal recovery occurred (defined as a decrease in creatinine level and a return of spontaneous urine output to >1000 ml per 24 hours [or >2000 ml per 24 hours in patients receiving diuretics]).

The choice of renal-replacement therapy technique (intermittent or continuous) was at the discretion of clinical experts at each site, but participating clinicians were required to adhere to protocol instructions for settings and monitoring, which were based on international guidelines[17,18] (see Table S3 in the Supplementary Appendix). In both groups, discontinuation of renal-replacement therapy was considered if renal recovery occurred, as defined above.

TRIAL OUTCOMES

The primary outcome was death from any cause at 90 days after randomization. Secondary outcomes were death at 28 days and at 180 days; the number of days free of renal-replacement therapy, mechanical ventilation, and vasopressors at 28 days after randomization; the length of stay in the ICU and in the hospital; adverse events during the entire ICU stay, with a focus on the complications potentially related to acute kidney injury or renal-replacement therapy during the first 7 days after enrollment; fluid balance in the first 7 days after enrollment; the need for emergency renal-replacement therapy in the delayed-strategy group; death of patients in the delayed-strategy group in whom at least one criterion for emergency renal-replacement therapy was met; and dependence on renal-replacement therapy at hospital discharge.

STATISTICAL ANALYSIS

Considering that death at 90 days was a binary outcome and assuming that mortality would be 10 percentage points lower in the early-strategy group than in the delayed-strategy group (45% vs. 55%) and that 5% of the patients would not be able to be evaluated, we estimated that 864 patients (432 per group) would need to be enrolled to provide 80% power at a two-sided alpha level of 0.05. Two interim efficacy analyses were planned (see the Interim Analyses section in the Supplementary Appendix). In both interim analyses, the frequency of death at 90 days after randomization in the two groups was compared with the chi-square test, at an alpha level of 0.0001[19]

to avoid changing the level of significance of the final primary analysis.

The primary analysis was performed according to the intention-to-treat principle. Categorical variables are expressed as numbers and percentages; continuous variables are expressed as means and standard deviations or medians and interquartile ranges as appropriate. Both categorical and continuous variables were compared in bivariate analyses with the use of corresponding tests. For the main comparison between the two groups of the proportion of deaths at 90 days, we used a chi-square test. A logistic-regression analysis with further stratification according to center was performed with adjustment for baseline prognostic factors (the presence or absence of chronic renal failure and exposure or nonexposure to hydroxyethyl starch in the 24 hours before randomization).

In secondary analyses, the proportion of deaths at 28 days and at 180 days was assessed and the corresponding survival probabilities were plotted with the use of the Kaplan–Meier method. The time from documentation of acute kidney injury to initiation of renal-replacement therapy, the length of ICU and hospital stay, and the number of days free of mechanical ventilation, vasopressors, and renal-replacement therapy are expressed as medians and interquartile ranges and were compared with the use of the Mann–Whitney test. We evaluated safety by calculating the percentage of patients in the two groups in whom the criteria for emergency renal-replacement therapy were met and the percentage with severe metabolic disorders, pulmonary edema due to fluid overload, arterial hypotension requiring an increase in vasopressor dose or a reintroduction of vasopressors, severe symptomatic cardiac arrhythmias, and severe hemorrhage; percentages were compared with the use of appropriate tests.

Analyses were performed with SAS software, version 9.3 (SAS Institute). The significance level was set at 0.05 for all analyses. Given the negative primary outcome, secondary outcomes should be regarded as exploratory and should not be used for inferences about treatment differences.

RESULTS

ENROLLMENT

The trial was conducted from July 2012 through October 2016 in 29 ICUs (22 university teaching hospitals and 7 general hospitals) in France. A total of 1728 of the patients who were assessed were eligible for inclusion, of whom 488 underwent randomization; 246 patients were assigned to the early-strategy group and 242 to the delayed-strategy group (Fig. 1). After the second interim analysis, the independent data and safety monitoring board deemed that completion of enrollment was unlikely to change the results of the trial significantly and recommended that the trial be stopped. The conditional power calculated at the second interim analysis, when termination of the trial owing to futility was recommended, was 51.44% (details are provided in the Interim Analyses section in the Supplementary Appendix).

BASELINE CHARACTERISTICS

There were no significant differences in baseline characteristics between the groups (Table 1, and Table S4 in the Supplementary Appendix). In addition, diagnostic criteria for acute kidney injury did not differ between the two groups. The frequency of chronic renal failure was higher in the delayed-strategy group, and exposure to nephrotoxic agents was higher in the early-strategy group, but neither difference was significant.

INITIATION OF RENAL-REPLACEMENT THERAPIES

Nearly all patients assigned to the early-strategy group received renal-replacement therapy (239 of 246 patients [97%]). In the delayed-strategy group, 149 of 242 patients (62%) received renal-replacement therapy; of the remaining 93 patients, 70 (29%) did not receive renal-replacement therapy because they had spontaneous recovery of renal function, 21 (8%) died before renal-replacement therapy was initiated, and 2 (1%) did not receive renal-replacement therapy for other reasons (Table S5 in the Supplementary Appendix).

The median time from diagnosis of acute kidney injury to initiation of renal-replacement therapy was 7.6 hours (interquartile range, 4.4 to 11.5) in the early-strategy group and 51.5 hours (interquartile range, 34.6 to 59.5) in the delayed-strategy group (P<0.001). Criteria for emergency renal-replacement therapy were met in 41 patients in the delayed-strategy group (17%), who thus received renal-replacement therapy before the 48-hour delay had taken place. Patient characteristics at the time of initiation of renal-replacement therapy are provided in Table S6 in the Supplementary Appendix.

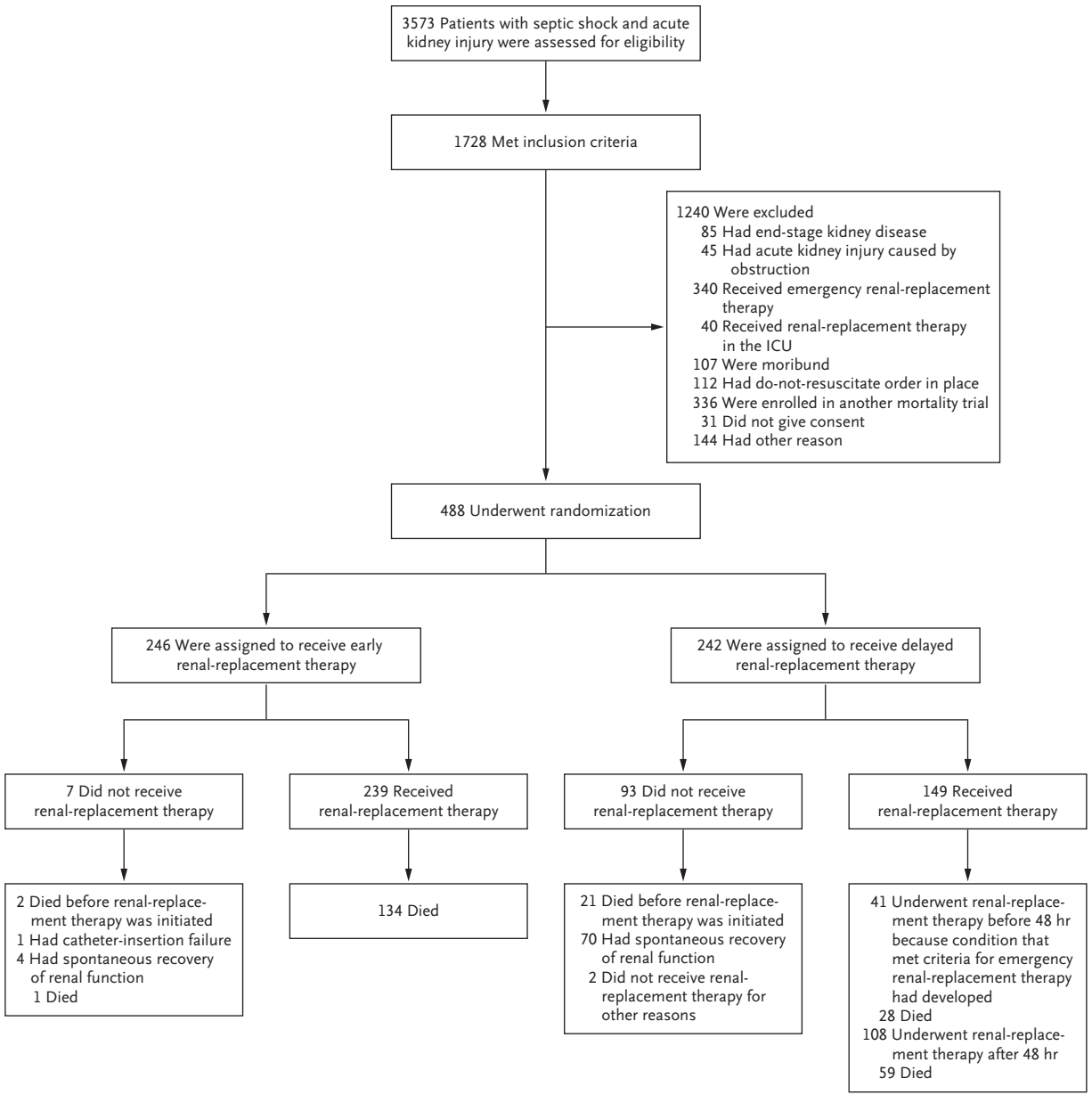

Figure 1. Screening, Randomization, and Follow-up.
ICU denotes intensive care unit.

PRIMARY OUTCOME

Follow-up data at 90 days were available for 477 patients (98%). The early initiation of renal-replacement therapy did not result in lower mortality at 90 days than the delayed strategy; 138 of 239 patients (58%) in the early-strategy group died and 128 of 238 patients (54%) in the delayed-strategy group died (P=0.38) (Table 2). Further stratification according to center and adjustment for preexisting chronic renal failure and exposure to nephrotoxic agents did not change the results.

SECONDARY OUTCOMES

The delayed strategy resulted in a significantly larger number of days free of renal-replacement

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Early Strategy (N=246)	Delayed Strategy (N=242)
Age — yr	69.3±11.6	68.7±12.8
Sex — no. (%)		
Male	142 (58)	154 (64)
Female	104 (42)	88 (36)
Body-mass index†	28.8±7.7	29.0±8.3
Coexisting conditions — no. (%)		
Chronic renal failure	32 (13)	44 (18)
Hypertension	145 (59)	137 (57)
Diabetes	80 (33)	69 (29)
Congestive heart failure‡	20 (8)	20 (8)
Chronic respiratory failure	19 (8)	10 (4)
Chronic liver disease	31 (13)	31 (13)
Immunosuppression	69 (28)	74 (31)
Median days in hospital before ICU admission (IQR)	1 (1–2)	1 (1–3)
SAPS II at ICU admission§	65.1±16.5	64.1±15.6
SOFA score at enrollment¶	12.2±2.9	12.4±2.9
Exposure to at least one nephrotoxic agent within 4 days before randomization — no. (%)	128 (52)	106 (44)
Multiple organ support in ICU — no. (%)		
Invasive mechanical ventilation	219 (89)	213 (88)
Vasopressor support with norepinephrine or epinephrine	246 (100)	242 (100)
Inotropic support with dobutamine	52 (21)	58 (24)
Extracorporeal membrane oxygenation	1 (<1)	9 (4)
Diagnostic criteria for acute kidney injury at the failure stage of the RIFLE classification — no. (%)‖		
Oliguria	86 (35)	80 (33)
Anuria	83 (34)	88 (36)
Serum creatinine 3 times the baseline level**	156 (63)	149 (62)
Serum creatinine before ICU admission — mg/dl**	1.01±0.49	1.06±0.50
Serum creatinine at enrollment — mg/dl	3.21±1.48	3.40±1.60
Blood urea nitrogen — mg/dl	59.2±26.9	63.1±30.0
Serum potassium — mmol/liter	4.3±0.8	4.5±0.9
Serum bicarbonate — mmol/liter	17.7±5.0	17.7±4.5
Fluid balance before enrollment — ml/24 hr	3194±2352	3211±2244

* Plus–minus values are means ±SD. There were no significant between-group differences in the characteristics at baseline. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for blood urea nitrogen to millimoles per liter, multiply by 0.357. ICU denotes intensive care unit, and IQR interquartile range.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ This category includes patients who had a New York Heart Association class of III or IV.

§ The Simplified Acute Physiology Score (SAPS) II ranges from 0 to 163, 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.

‖ The failure stage of the risk, injury, failure, loss, and end-stage kidney disease (RIFLE) classification is defined as a serum creatinine level 3 times the baseline level (or ≥4 mg per deciliter with a rapid increase of ≥0.5 mg per deciliter), oliguria (urine output <0.3 ml per kilogram of body weight per hour for ≥24 hours), or anuria for 12 hours or more.

** The baseline serum creatinine level either was determined with the use of values measured in the 12 months preceding the ICU stay or was estimated.

therapy (median days, 16; interquartile range, 2 to 28) than the early strategy (median days, 12; interquartile range, 1 to 25) (P=0.006). There were no significant differences between the groups in the other secondary outcomes, namely mortality at 28 days and 180 days, number of days free of mechanical ventilation and vasopressors, and length of ICU and hospital stay (Table 2, and Table S7 in the Supplementary Appendix). Overall survival estimated with the Kaplan–Meier method is shown in Figure 2. The rate of dependence on renal-replacement therapy among survivors at 28 days did not differ significantly between the groups (13% in the early-strategy group and 12% in the delayed-strategy group; P=0.89). Details of renal-replacement therapy techniques and settings are provided in Table S8 in the Supplementary Appendix.

SAFETY

In the delayed-strategy group, a condition meeting at least one criterion for emergency renal-replacement therapy developed in 41 patients (17%); 28 of these patients died. Metabolic abnormalities observed in the first 7 days after enrollment were more common in the delayed-strategy group than in the early-strategy group; 9 patients (4%) in the delayed-strategy group had severe hyperkalemia (with a median potassium level of 7.0 mmol per liter [interquartile range, 6.7 to 7.3]), whereas no patients in the early-strategy group had hyperkalemia (P=0.03) (Table 3). There were no significant differences between the groups in other adverse events.

FLUID BALANCE

There was no significant difference between the groups in fluid balance in the 24 hours before randomization, in the 48 hours after enrollment, or at 7 days. Details are provided in Table S9 in the Supplementary Appendix.

DISCUSSION

Our trial addressed the question of the timing of renal-replacement therapy specifically in a homogeneous population of patients with severe acute kidney injury who were in the early phase of septic shock. In this population, a strategy of early initiation of renal-replacement therapy did not result in lower mortality at 90 days than a strategy in which initiation of renal-replacement therapy was delayed by 48 hours. There was less use of renal-replacement therapy in the delayed-strategy group; 38% of patients did not undergo renal-replacement therapy (75% of these patients had spontaneous recovery of renal function). The overall mortality was 55%, corresponding exactly to our working hypothesis, which was based on published data.[4-7]

Recently, two randomized, controlled trials[12,13] explored the question of the timing of initiation of renal-replacement therapy, but their results were conflicting. Our results are similar to those reported by Gaudry and colleagues,[12] who enrolled more than 600 patients who were admitted to the ICU with acute kidney injury of Kidney Disease: Improving Global Outcomes (KDIGO) classification stage 3 (serum creatinine 3 times the baseline level or ≥4 mg per deciliter, urine output <0.3 ml per kilogram per hour for ≥24 hours, or anuria for ≥12 hours; stages range from 1 to 3, with higher stages indicating more severe kidney injury); they found no significant difference in mortality at 60 days when comparing a strategy of early renal-replacement therapy with a delayed strategy in which renal-replacement therapy was initiated only if prespecified criteria were met. A post hoc analysis involving 348 patients with septic shock (56% of the overall population) had similar results.[20] The second trial[13] was a single-center, randomized, controlled trial that enrolled 231 patients with acute kidney injury of KDIGO stage 2 (serum creatinine level 2.0 to 2.9 times the baseline level or urine output <0.5 ml per kilogram per hour for ≥12 hours) and showed the opposite result — significantly lower mortality at 90 days in the group assigned to early initiation than in the group assigned to delayed initiation. Differences in inclusion criteria and dialysis techniques might explain the discrepancies in the results between that trial and our current trial.

The potential advantage of earlier initiation of dialysis in acute kidney injury is that it may improve acid–base, electrolyte, and fluid balance, thereby preventing more severe complications of acute kidney injury and perhaps also enhancing removal of toxins.[21] However, in our trial we did not observe lower mortality with early initiation than with delayed initiation. Thus, our results did not confirm our hypothesis that a strategy of early renal-replacement therapy could improve fluid balance and outcomes in this specific population. A possible explanation is that fluid removal with renal-replacement therapy cannot be

Table 2. Primary and Secondary Outcomes.*

Variable	Early Strategy (N=246)	Delayed Strategy (N=242)	P Value
Primary outcome			
Death at 90 days — no./total no. (%)	138/239 (58)	128/238 (54)	0.38
Secondary outcomes			
Death at 28 days — no. (%)	111 (45)	102 (42)	0.48
Death at 180 days — no./total no. (%)	143/236 (61)	134/235 (57)	0.37
Median time from diagnosis of failure-stage acute kidney injury to initiation of renal-replacement therapy (IQR) — hr†	7.6 (4.4–11.5)	51.5 (34.6–59.5)	<0.001
Patients who received renal-replacement therapy — no. (%)	239 (97)	149 (62)	<0.001
Patients in the delayed-strategy group who received emergency renal-replacement therapy before 48 hr, according to criterion — no. (%)‡		41 (17)	
Metabolic acidosis			
No. of patients (%)		20 (8)	
Median pH (IQR)		7.10 (7.06–7.13)	
Hyperkalemia			
No. of patients (%)		9 (4)	
Median potassium level (IQR) — mmol/liter		7.0 (6.7–7.3)	
Fluid overload — no. (%)		6 (2)	
Other criterion — no. (%)§		6 (2)	
Median days of renal-replacement therapy (IQR)	4 (2–8)	2 (0–6)	<0.001
Median days free of renal-replacement therapy (IQR)¶	12 (1–25)	16 (2–28)	0.006
Median days free of mechanical ventilation (IQR)¶	2 (0–19)	3 (0–21)	0.19
Median days free of vasopressors (IQR)¶	16 (0–25)	17 (0–25)	0.87
Median length of ICU stay (IQR) — days	11 (4–19)	10 (5–19)	0.91
Survivors	12 (8–21)	12 (8–21)	0.88
Nonsurvivors	5 (2–15)	6 (3–14)	0.64
Median length of hospital stay (IQR) — days	23 (10–40)	23 (10–44)	0.34
Survivors	22.0 (9.0–38.0)	21.0 (10.0–42.5)	0.53
Nonsurvivors	25 (15–53)	42 (33–56)	0.08
SOFA score without renal component‖			
Day 1	9.3±3.5	9.3±3.2	0.84
Day 2	8.6±3.8	8.4±3.9	0.57
Day 3	8.0±4.0	7.8±4.1	0.64
Day 7	5.9±3.8	6.3±3.9	0.30
Fluid balance — ml			
Cumulative fluid balance after day 2	3737±3925	3437±3371	0.40
Cumulative fluid balance at day 7	5570±8761	5878±7472	0.75
Receipt of diuretics from day 0 to 7			
No. of patients (%)	121 (49)	124 (51)	0.65
Median cumulative dose of furosemide from day 0 to 7 (IQR) — mg	215 (65–760)	295 (80–1160)	0.18
Dependence on renal-replacement therapy among survivors — no./total no. (%)			
Day 28	17/134 (13)	17/140 (12)	0.89
Day 90	2/101 (2)	3/110 (3)	1.00

Table 2. (Continued.)

Variable	Early Strategy (N=246)	Delayed Strategy (N=242)	P Value
Creatinine — mg/dl**			
At ICU discharge	2.00±1.26	2.19±1.47	0.15
At hospital discharge	1.46±0.98	1.61±1.30	0.31

* Plus–minus values are means ±SD.
† Acute kidney injury in failure stage was defined according to the RIFLE classification.
‡ This category includes patients in the delayed-strategy group who met criteria for emergency renal-replacement therapy. Metabolic acidosis was defined as a pH less than 7.15 and a base deficit of more than 5 mmol per liter or a bicarbonate level of 18 mmol or less per liter. Hyperkalemia was defined as a potassium level of more than 6.5 mmol per liter with characteristic electrocardiographic changes. The median pH and median potassium values were calculated only in patients who underwent renal-replacement therapy because they met these specific criteria. Fluid overload was defined as extravascular fluid overload that was refractory to diuretics, with pulmonary edema. Other reasons included worsening of the patient's clinical status, with acidosis and hyperkalemia below the prespecified threshold, associated with hyperlactatemia, with the need for emergency renal-replacement therapy as determined by the clinician treating the patient.
§ Other criterion was worsening of multiple organ failure that mandated the initiation of renal-replacement therapy in the opinion of the clinician caring for the patient, confirmed by an increase of at least 2 points in the SOFA score (not a prespecified criterion for emergency renal-replacement therapy).
¶ The number of days free of renal-replacement therapy, mechanical ventilation, or vasopressor therapy was calculated according to the number of days the patient was alive without the intervention at day 28; patients who died were assigned zero free days.
‖ In patients who received renal-replacement therapy, the renal component of the SOFA score was calculated on the basis of urine output only.
** Creatinine values are for all living patients who were no longer receiving renal-replacement therapy.

performed easily or safely in patients with hemodynamic instability in the early phases of septic shock, so starting such therapy earlier would not improve fluid balance.

Our results show that initiating renal-replacement therapy too early could unnecessarily expose patients in whom renal dysfunction would have recovered spontaneously to the risks associated with renal-replacement therapy. Indeed, 29% of the patients in the delayed-strategy group did not require renal-replacement therapy because they had spontaneous recovery of renal function, although 26% of these patients (18 of 70 patients) subsequently died, which is similar to rates reported in other studies.[22] It is possible that more patients might have recovered without renal-replacement therapy if the delay had been longer than 48 hours, as was observed in a recent study.[12] Mortality was higher among patients assigned to the delayed-strategy group who met criteria for emergency renal-replacement therapy (68% [28 of 41 patients]) than among those who did not meet the criteria. However, the development of these complications may be identifying a subgroup of patients with more severe underlying disease, and we cannot conclude that death was related to the delay in renal-replacement therapy or that earlier initiation of renal-replacement therapy would have saved a given patient.

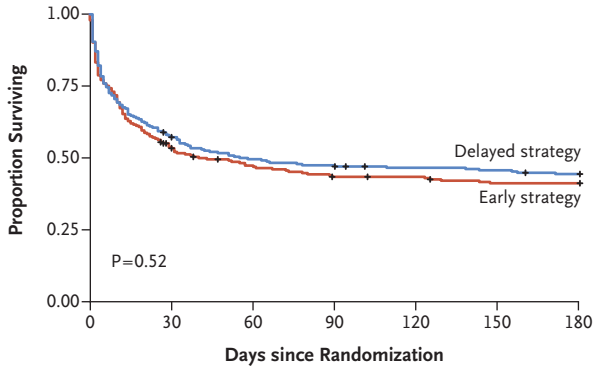

Figure 2. Overall Survival among Patients Assigned to Early Renal-Replacement Therapy and Delayed Renal-Replacement Therapy.
In the early-strategy group, renal-replacement therapy was initiated within 12 hours after documentation of acute kidney injury. In the delayed-strategy group, renal-replacement therapy was initiated 48 hours after the documentation of acute kidney injury, if renal recovery had not occurred. If criteria for emergency renal-replacement therapy were met by a patient in this group, renal-replacement therapy was initiated as soon as possible. The tick marks indicate censored data. The P value is for the comparison of overall survival between the two groups.

Although our trial did not show any benefit to expediting the initiation of renal-replacement therapy in the absence of emergency criteria, our

Table 3. Complications and Adverse Events.

Complication or Adverse Event	Early Strategy (N=246)	Delayed Strategy (N=242)	P Value
Complications potentially related to acute kidney injury or renal-replacement therapy in the first 7 days after enrollment			
Metabolic acidosis*			
No. of patients (%)	22 (9)	40 (17)	0.07
Median pH (IQR)	7.1 (7.1–7.1)	7.1 (7.0–7.1)	0.36
Hyperkalemia†			
No. of patients (%)	0	10 (4)	0.03
Median potassium level (IQR) — mmol/liter	—	7.0 (6.7–7.3)	—
Fluid overload — no. of patients (%)‡	1 (<1)	9 (4)	0.16
Severe cardiac-rhythm disorder — no. of patients (%)§	23 (10)	13 (5)	0.77
Symptomatic bradycardia	15 (6)	11 (4)	0.67
Ventricular tachycardia or ventricular fibrillation	10 (4)	3 (1)	0.25
Severe bleeding event¶			
No. of patients (%)	12 (5)	15 (6)	0.52
Median volume of packed red cells transfused per patient (IQR) — units	4.0 (3.5–7.0)	5.0 (3.0–7.0)	0.98
Hypotensive episode during renal-replacement therapy‖			
No. of patients/total no. (%)	86/239 (36)	57/149 (38)	0.62
Median mean arterial pressure of the most severe episode (IQR)	47 (40–52)	44 (36–52)	0.40
Other adverse events that occurred during the trial — no. of patients (%)			
Other cardiovascular complication	94 (38)	95 (39)	0.81
New infection	55 (22)	44 (18)	0.25
Respiratory complication	25 (10)	36 (15)	0.11
Gastrointestinal complication	32 (13)	25 (10)	0.36
Neurologic complication	29 (12)	20 (8)	0.19
Thrombotic or embolic complication	13 (5)	14 (6)	0.81
Minor bleeding event¶	52 (21)	53 (22)	0.84
Other hematologic complication	22 (9)	23 (10)	0.83
Other metabolic complication**	9 (4)	8 (3)	0.83

* Metabolic acidosis was defined as a pH of less than 7.15 and a base deficit of more than 5 mmol per liter or a bicarbonate level of 18 mmol or less per liter.
† Hyperkalemia was defined as a potassium level of more than 6.5 mmol per liter with characteristic electrocardiographic changes.
‡ Fluid overload was defined as extravascular fluid overload that was refractory to diuretics with pulmonary edema.
§ Severe cardiac-rhythm disorders were defined as ventricular tachycardia, ventricular fibrillation, torsades de pointes, third-degree atrioventricular block, or extreme bradycardia requiring medical treatment.
¶ Severe bleeding events were defined as the need for transfusion of 3 or more consecutive units of packed red cells in the same day. Minor bleeding events were defined as the need for transfusion of less than 3 units of packed red cells in the same day.
‖ Hypotensive episodes during renal-replacement therapy were defined as a mean arterial pressure of 55 mm Hg or less and an increase in vasopressor dose or a reintroduction of vasopressors. The frequency of this adverse event was calculated only in patients who underwent renal-replacement therapy.
** Other metabolic complications were defined as severe hypophosphatemia (serum phosphate <0.5 mmol per liter [<1.5 mg per deciliter]) or severe hypoglycemia (glucose <2.8 mmol per liter [<50 mg per deciliter]).

results cannot be interpreted as encouraging indefinite deferral of renal-replacement therapy. Rather, our data indicate that the risk of death is not increased if renal-replacement therapy is postponed for at least 48 hours, as long as care is taken to identify patients in whom criteria for emergency renal-replacement therapy are likely to be met.

Our trial has certain limitations. First, we used the failure stage of the RIFLE classification to identify eligible patients. RIFLE was the most commonly used classification for the identification of patients with acute kidney injury at the time the trial was designed. However, studies have shown that RIFLE is not as sensitive as the most recent classification system. Moreover, the failure stage was not necessarily intended to identify patients who would require renal-replacement therapy. The second limitation is the choice of a delay of only 48 hours, which may not be sufficiently long to allow recovery of renal function in some patients or to detect a difference between early and delayed initiation of renal-replacement therapy. However, we thought that a longer delay would be unethical and unsafe for patients who actually needed renal-replacement therapy.

In conclusion, this trial showed no significant difference in mortality between a strategy of early initiation of renal-replacement therapy and a strategy of delayed initiation in patients with septic shock and severe acute kidney injury but with no immediate, life-threatening complications linked to acute kidney injury.

Supported by a grant (A00519-34) from the Programme Hospitalier de Recherche Clinique National, funded by the French Ministry of Health.

Dr. Jaber reports receiving consulting fees from Dräger Medical, Fisher and Paykel, and Xenios; and Dr. Roger, receiving travel support from MSD and Pfizer. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the staff in the participating ICUs; the clinical research assistants for data entry; Alexandra Felin, project leader (INSERM Centre d'Investigation Clinique–Epidémiologie Clinique 1432, Dijon, France); and Fiona Ecarnot (EA3920, University Hospital, Besançon, France) for translation and critical revision.

APPENDIX

The authors' full names and academic degrees are as follows: Saber D. Barbar, M.D., Ph.D., Raphaël Clere-Jehl, M.D., Abderrahmane Bourredjem, M.Sc., Romain Hernu, M.D., Florent Montini, M.D., Rémi Bruyère, M.D., Christine Lebert, M.D., Julien Bohé, M.D., Ph.D., Julio Badie, M.D., Jean-Pierre Eraldi, M.D., Jean-Philippe Rigaud, M.D., Ph.D., Bruno Levy, M.D., Ph.D., Shidasp Siami, M.D., Ph.D., Guillaume Louis, M.D., Lila Bouadma, M.D., Ph.D., Jean-Michel Constantin, M.D., Ph.D., Emmanuelle Mercier, M.D., Kada Klouche, M.D., Ph.D., Damien du Cheyron, M.D., Ph.D., Gaël Piton, M.D., Ph.D., Djillali Annane, M.D., Ph.D., Samir Jaber, M.D., Ph.D., Thierry van der Linden, M.D., Ph.D., Gilles Blasco, M.D., Jean-Paul Mira, M.D., Ph.D., Carole Schwebel, M.D., Ph.D., Loïc Chimot, M.D., Philippe Guiot, M.D., Mai-Anh Nay, M.D., Ferhat Meziani, M.D., Ph.D., Julie Helms, M.D., Ph.D., Claire Roger, M.D., Ph.D., Benjamin Louart, M.D., Remi Trusson, M.D., Auguste Dargent, M.D., Christine Binquet, M.D., Ph.D., and Jean-Pierre Quenot, M.D., Ph.D.

The authors' affiliations are as follows: Réanimation Médicale, Centre Hospitalier Universitaire (CHU) de Nîmes (S.D.B., B. Louart, R.T.), and Saint Eloi, CHU de Montpellier, Université de Montpellier, and INSERM Unité 1046 (S.J.), Service de Réanimation Médicale, CHU Lapeyronie (K.K.), Montpellier, Université de Strasbourg, Faculté de Médecine, Hôpitaux Universitaires de Strasbourg, Service de Réanimation, Nouvel Hôpital Civil, Strasbourg (R.C.-J., F. Meziani, J.H.), Service de Médecine Intensive Réanimation, Hôpital Universitaire François Mitterrand, and Lipness Team, INSERM Research Center Lipids, Nutrition, Cancer–Unité Mixte de Recherche 1231 and Laboratoire d'Excellence LipSTIC (A.D., J.-P.Q.), and Centre d'Investigation Clinique–Epidemiologie Clinique, CHU Dijon-Bourgogne and INSERM Centre d'Investigation Clinique 1432, Université de Bourgogne, Dijon (A.B., C.B., J.-P.Q.), Réanimation Médicale, Hôpital Edouard Herriot, Hospices Civils de Lyon, Lyon (R.H.), Réanimation Polyvalente, Centre Hospitalier d'Avignon, Avignon (F. Montini), Réanimation Polyvalente, Centre Hospitalier de Bourg-en-Bresse, Bourg-en-Bresse (R.B.), Service de Médecine Intensive-Réanimation, Centre Hospitalier de La Roche-sur-Yon, La Roche-sur-Yon (C.L.), Intensive Care Unit, Hospices Civils de Lyon, Centre Hospitalier Lyon-Sud, Pierre-Bénite (J. Bohé), Réanimation Polyvalente, Hôpital Nord Franche-Comté, Belfort (J. Badie), Médecine Intensive Réanimation, Centre Hospitalier de Dieppe, Dieppe (J.-P.E., J.-P.R.), Service de Réanimation Médicale, CHU de Nancy-Brabois, Nancy (B. Levy), Service d'Anesthésie–Réanimation, Centre Hospitalier d'Etampes, Etampes (S.S.), Réanimation Polyvalente, Hôpital Bon Secours, Centre Hospitalier Régional de Metz, Metz (G.L.), Infection, Antimicrobiens, Modélisation, Evolution, Unité 1137, Team Decision Sciences in Infectious Disease Prevention, Control, and Care, Université Paris Diderot, Sorbonne Paris Cité, and Medical and Infectious Diseases ICU, Bichat–Claude-Bernard Hospital, Assistance Publique–Hôpitaux de Paris (L.B.), and Service de Réanimation Médicale, Hôpital Cochin (J.-P.M.), Paris, Pôle de Médecine Péri-Opératoire, GReD, and INSERM Unité 1103, CHU Clermont-Ferrand, Clermont-Ferrand (J.-M.C.), Service de Réanimation Médicale, CHU Régional de Tours, Tours (E.M.), CHU de Caen, Service de Réanimation Médicale, Caen (D.C.), Service de Réanimation Médicale (G.P.) and Service de Réanimation Chirurgicale (G.B.), CHU de Besançon, Besançon, Service de Médecine Intensive et Réanimation, Hôpital Raymond Poincaré, Garches (D.A.), Laboratory of Infection and Inflammation, INSERM Unité 1173, University of Versailles Saint-Quentin-en-Yvelines, Montigny-le-Bretonneux (D.A.), Service de Médecine Intensive Réanimation, Groupe des Hôpitaux de l'Institut Catholique de Lille, Université Catholique de Lille, Lille (T.L.), Service de Réanimation Médicale, CHU de Grenoble, Grenoble (C.S.), Service de Réanimation, Centre Hospitalier de Perigueux, Perigueux (L.C.), Service de Réanimation Polyvalente, Centre Hospitalier Général de Mulhouse, Mulhouse (P.G.), Médecine Intensive Réanimation, Centre Hospitalier Régional d'Orléans, Orléans (M.-A.N.), and Réanimation Chirurgicale–CHU de Nîmes, Nîmes (C.R.) — all in France.

REFERENCES

1. Hoste EA, Bagshaw SM, Bellomo R, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med 2015;41:1411-23.
2. Mehta RL, Cerdá J, Burdmann EA, et al. International Society of Nephrology's 0by25 initiative for acute kidney injury (zero preventable deaths by 2025): a human rights case for nephrology. Lancet 2015;385:2616-43.
3. Quenot JP, Binquet C, Kara F, et al. The epidemiology of septic shock in French intensive care units: the prospective multicenter cohort EPISS study. Crit Care 2013;17:R65.
4. Bagshaw SM, George C, Bellomo R. Early acute kidney injury and sepsis: a multicentre evaluation. Crit Care 2008;12:R47.
5. The RENAL Replacement Therapy Study Investigators. Intensity of continuous renal-replacement therapy in critically ill patients. N Engl J Med 2009;361:1627-38.
6. The VA/NIH Acute Renal Failure Trial Network. Intensity of renal support in critically ill patients with acute kidney injury. N Engl J Med 2008;359:7-20.
7. Uchino S, Kellum JA, Bellomo R, et al. Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 2005;294:813-8.
8. Dellepiane S, Marengo M, Cantaluppi V. Detrimental cross-talk between sepsis and acute kidney injury: new pathogenic mechanisms, early biomarkers and targeted therapies. Crit Care 2016;20:61.
9. Bellomo R, Kellum JA, Ronco C, et al. Acute kidney injury in sepsis. Intensive Care Med 2017;43:816-28.
10. Payen D, Mateo J, Cavaillon JM, Fraisse F, Floriot C, Vicaut E. Impact of continuous venovenous hemofiltration on organ failure during the early phase of severe sepsis: a randomized controlled trial. Crit Care Med 2009;37:803-10.
11. Piccinni P, Dan M, Barbacini S, et al. Early isovolaemic haemofiltration in oliguric patients with septic shock. Intensive Care Med 2006;32:80-6.
12. Gaudry S, Hajage D, Schortgen F, et al. Initiation strategies for renal-replacement therapy in the intensive care unit. N Engl J Med 2016;375:122-33.
13. Zarbock A, Kellum JA, Schmidt C, et al. 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. JAMA 2016;315:2190-9.
14. Barbar SD, Binquet C, Monchi M, Bruyère R, Quenot JP. 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. Trials 2014;15:270.
15. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure — definition, outcome measures, animal models, fluid therapy and information technology needs. Crit Care 2004;8:R204-R212.
16. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med 1996;22:707-10.
17. Brochard L, Abroug F, Brenner M, et al. An official ATS/ERS/ESICM/SCCM/SRLF statement: Prevention and Management of Acute Renal Failure in the ICU Patient: an international consensus conference in intensive care medicine. Am J Respir Crit Care Med 2010;181:1128-55.
18. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl 2012;2:1-138.
19. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. Br J Cancer 1976;34:585-612.
20. Gaudry S, Hajage D, Schortgen F, et al. Timing of renal support and outcome of septic shock and acute respiratory distress syndrome: a post hoc analysis of the AKIKI randomized clinical trial. Am J Respir Crit Care Med 2018;198:58-66.
21. Wald R, Bagshaw SM. The timing of renal replacement therapy initiation in acute kidney injury: is earlier truly better? Crit Care Med 2014;42:1933-4.
22. Wald R, Adhikari NK, Smith OM, et al. Comparison of standard and accelerated initiation of renal replacement therapy in acute kidney injury. Kidney Int 2015;88:897-904.

CLINICAL TRIAL REGISTRATION

The *Journal* requires investigators to register their clinical trials in a public trials registry. The members of the International Committee of Medical Journal Editors (ICMJE) will consider most reports of clinical trials for publication only if the trials have been registered. Current information on requirements and appropriate registries is available at www.icmje.org/about-icmje/faqs/.