Initiation Strategies for Renal Replacement Therapy in ICU

The Artificial Kidney Initiation in Kidney Injury trial

AKIKI

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Hôpital Louis Mourier, Colombes
Sorbonne-Paris-Cité University
Conflict of interest

Educational grants from Xenios France

No conflict of interest regarding RRT

AKIKI study funded by a grant from French Ministry of Health
When to start?

THE LANCET
JANUARY 21, 1961

OPTIMUM TIME FOR DIALYSIS IN ACUTE REVERSIBLE RENAL FAILURE
Description and Value of an Improved Dialyser with Large Surface Area

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M.B., B.Sc. Leeds
ASSISTANT DIRECTOR
METABOLIC DISTURBANCES IN SURGERY (M.R.C.) UNIT

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TECHNICAL ASSISTANT

B. H. McCracken
M.D. Wisconsin, M.R.C.P.
LATELY LECTURER*

From the General Infirmary at Leeds
Available data on the timing

Observational studies

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


Victor F. Seabra, MD,¹ Ethan M. Balk, MD, MPH,² Orfeas Liangos, MD,³ Marie Anne Sosa, MD,³ Miguel Cendoroglo, MD,⁴ and Bertrand L. Jaber, MD, MS³

Cohort studies

1961
1963
1963
1966
1965
1970
1971
1972

N=270
N=2118

Early RRT
Delayed RRT
Patients with AKI

- Patients managed with RRT
  - Early RRT initiation
  - Late RRT initiation
  - No RRT
Patients with AKI

Patients managed with RRT

Early RRT initiation

Late RRT initiation

No RRT

Observational studies
Patients with AKI

- Early RRT strategy:
  - Receive RRT

- Late RRT strategy:
  - Receive RRT
  - No RRT

Study design to adequately answer clinical question of timing of RRT in AKI
Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit

Stéphane Gaudry, M.D., David Hajage, M.D., Frédérique 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*
Financial Support

Supported by the Programme Hospitalier de Recherche Clinique (PHRC) National, 2012 (AOM12456), funded by the French Ministry of Health
AKII Design

- Multicenter open-label two-arm randomized trial

- Ethics and patient information
  - Approved by the ethical committee of French Society of Intensive Care and by the competent French legal authority (CPP)
  - Full patient and/or surrogate information
  - Possibility of randomization through a process of deferred information

- 31 ICUs in France

- September 2013 - January 2016
Inclusion Criteria

• Adults

• Invasive MV and/or catecholamine infusion

• AKI Stage 3 of KDIGO classification
  – Serum creatinine 3.0 times baseline or > 354 µmol/l (4.0 mg/dl)
  – or Urine output <0.3 ml/kg/h for 24 hours
  – or Anuric for ≥12 hours
Study Interventions

Early Strategy Group

RRT as soon as possible

Within 6 hours after inclusion criteria

Delayed Strategy Group

RRT only if pre-specified criteria present
• Severe hyperkalemia
  potassium > 6 mmol/l, or > 5.5 mmol/l *Despite medical treatment*

• Severe acidosis (pH <7.15)

• Acute pulmonary edema due to fluid overload
  *Responsible for severe hypoxemia*

• Oliguria/Anuria >72 hours

• Serum urea concentration > 40mmol/l
The choice of **RRT modality** was left to the discretion of each study site.
Primary outcome

Overall survival measured from the randomization date until death or day 60
Statistical analysis

- Sequential (2 interim analyses) study
- Expected mortality at day 60: 55%
- Hypothesis: 15% absolute decrease in mortality with delayed RRT strategy

Planned enrollment: 620 patients
5528 Had AKI and received vasoactive agent and/or invasive MV

3430 Had AKI stage 3 of KDIGO classification

620 Underwent randomization

Early RRT Strategy  
\( n=312 \)

Delayed RRT Strategy  
\( n=308 \)

1 patient refused the use of data

619 Were included in the analysis
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Early RRT strategy (N=311)</th>
<th>Delayed RRT strategy (N=308)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age – yr</strong></td>
<td>64.8±14.2</td>
<td>67.4±13.4</td>
</tr>
<tr>
<td><strong>SAPS III</strong></td>
<td>72.6±14.4</td>
<td>73.7±14.2</td>
</tr>
<tr>
<td><strong>Nephrotoxic agent in past 2 days – no. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous contrast</td>
<td>194 (63)</td>
<td>195 (65)</td>
</tr>
<tr>
<td>Aminoglycoside</td>
<td>66</td>
<td>71</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>106</td>
<td>106</td>
</tr>
<tr>
<td></td>
<td>26</td>
<td>29</td>
</tr>
<tr>
<td><strong>Physiological support – no. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive MV</td>
<td>266 (86)</td>
<td>267 (87)</td>
</tr>
<tr>
<td>Vasopressor support</td>
<td>265 (85)</td>
<td>263 (86)</td>
</tr>
<tr>
<td><strong>Sepsis status – no. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>25 (8)</td>
<td>21 (7)</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>16 (5)</td>
<td>19 (6)</td>
</tr>
<tr>
<td>Septic shock</td>
<td>209 (67)</td>
<td>204 (66)</td>
</tr>
<tr>
<td><strong>Biological characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine – micromoles/L</td>
<td>287±124</td>
<td>283±117</td>
</tr>
<tr>
<td>Serum urea– mmol/L</td>
<td>19±9</td>
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</tr>
<tr>
<td>Serum potassium – mmol/L</td>
<td>4.4±0.7</td>
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</tr>
<tr>
<td>Serum bicarbonate – mmol/L</td>
<td>18.7±5.1</td>
<td>18.8±5.5</td>
</tr>
</tbody>
</table>
Early RRT strategy

Delayed RRT strategy

p-value: <0.001

Days

Patients free of RRT

Proportion of patients free of RRT

Earliest RRT strategy

Delayed RRT strategy
A survival analysis comparing two strategies: Early RRT strategy and Delayed RRT strategy. The graph shows the proportion of survivors over days, with a p-value of 0.79, indicating no significant difference between the two strategies.
To detect an effect size of 1.2 %
(i.e., the difference in mortality that we found between the two groups)

with a power of 90%:

> 70,000 patients would be required
## Characteristics of RRT sessions

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<tr>
<td><strong>First modality— no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Intermittent RRT</td>
<td>169 (56)</td>
<td>86 (55)</td>
<td>0.97</td>
</tr>
<tr>
<td>Continuous RRT</td>
<td>135 (44)</td>
<td>71 (45)</td>
<td></td>
</tr>
<tr>
<td><strong>RRT modalities during ICU stay— no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermittent RRT only</td>
<td>142 (47)</td>
<td>73 (47)</td>
<td>0.62</td>
</tr>
<tr>
<td>Continuous RRT only</td>
<td>101 (33)</td>
<td>47 (30)</td>
<td></td>
</tr>
<tr>
<td>Both modalities</td>
<td>61 (20)</td>
<td>37 (24)</td>
<td></td>
</tr>
<tr>
<td><strong>Total number of RRT sessions</strong></td>
<td>1665</td>
<td>943</td>
<td></td>
</tr>
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## Secondary outcomes

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<td><strong>RRT-free days – median (IQR) day 28</strong></td>
<td>17 (2-26)</td>
<td>19 (5-29)</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>Catheter-related bloodstream infection – no. (%)</strong></td>
<td>31 (10)</td>
<td>16 (5)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Hypophosphatemia – no. (%)</strong></td>
<td>69 (23)</td>
<td>46 (16)</td>
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<td>69 (23)</td>
<td>46 (16)</td>
<td>0.03</td>
</tr>
<tr>
<td>Ventilator-free days – median (IQR) day 28</td>
<td>7 (0-22)</td>
<td>6 (0-21)</td>
<td>0.76</td>
</tr>
<tr>
<td>Vasopressor-free days – median (IQR) day 28</td>
<td>20 (1-26)</td>
<td>20 (0-26)</td>
<td>0.67</td>
</tr>
<tr>
<td>Length of ICU stay – median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survivors</td>
<td>13 (8-23)</td>
<td>13 (7-23)</td>
<td>0.87</td>
</tr>
<tr>
<td>Nonsurvivors</td>
<td>6 (2-14)</td>
<td>6 (2-13)</td>
<td>0.92</td>
</tr>
<tr>
<td>Length of hospital stay – median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survivors</td>
<td>29 (17-51)</td>
<td>32 (20-51)</td>
<td>0.58</td>
</tr>
<tr>
<td>Nonsurvivors</td>
<td>6 (2-14)</td>
<td>6 (2-13)</td>
<td>0.85</td>
</tr>
<tr>
<td>RRT dependence – no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At day 28</td>
<td>22 (13)</td>
<td>17 (10)</td>
<td>0.51</td>
</tr>
<tr>
<td>At day 60</td>
<td>3 (2)</td>
<td>8 (5)</td>
<td>0.12</td>
</tr>
</tbody>
</table>
Time to renal function recovery?
Adequate urine output with no need for RRT

Days

Early RRT strategy
Delayed RRT strategy

p-value: <0.001

311 99 42 27 10
308 68 29 14 7
Spontaneous creatinine decrease

No. at Risk

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<tr>
<th>Days</th>
<th>Early RRT strategy</th>
<th>Delayed RRT strategy</th>
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<tr>
<td>0</td>
<td>311</td>
<td>308</td>
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<tr>
<td>7</td>
<td>136</td>
<td>105</td>
</tr>
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<td>14</td>
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<td>26</td>
</tr>
<tr>
<td>28</td>
<td>14</td>
<td>16</td>
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p-value: 0.01
Limitations

• **Study power:**
  1.2% difference in mortality
  > 70,000 patients to show a significant difference

• **Dose of RRT**
  Not evaluated by KT/V *urea*
  Median BUN : < 21 mmol/l (60 mg/dl)

• **RRT modalities ?**
When you perform a 2 arm RCT you should compare the data according to groups of randomization.
Early RRT strategy

Receive RRT

Late RRT strategy

Receive RRT

No RRT

Post hoc analysis
Post hoc analysis

The comparison of the so-called subgroup of from delayed strategy group who actually received RRT with the “Early strategy” group is not interpretable.
Post hoc analysis

The **comparison of the so-called subgroup** of patients who actually received RRT with the “Early strategy” group **is not interpretable**

- **Indication bias**
  Patients who finally received RRT in the delayed strategy were those whose status worsened (time varying confounding)

- **Immortal time bias**
  It is not possible to identify a patient in the delayed strategy who will actually receive RRT at the time of inclusion, but only at the end of his/her follow-up
Looking for an interaction between SAPS 3 and RRT strategy (not excluding "no RRT" patients) is more appropriate
## Post-hoc analysis

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<th>Analysis</th>
<th>Population</th>
<th>HR</th>
<th>P Value</th>
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<tr>
<td>Raw data</td>
<td>Early Strategy (referent)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Delayed strategy RRT +</td>
<td>1.40 [1.08; 1.8]</td>
<td>0.01</td>
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<td>Delayed strategy <strong>No RRT</strong></td>
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<td>0.03</td>
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</tr>
<tr>
<td><strong>After matching (on SAPS III)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early Strategy (referent)</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delayed strategy RRT +</td>
<td><strong>1.24 [0.9; 1.7]</strong></td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>Delayed strategy No RRT</td>
<td><strong>0.83 [0.57; 1.21]</strong></td>
<td>0.34</td>
<td></td>
</tr>
</tbody>
</table>
Artificially dividing patients of the late strategy according to whether they received RRT or not makes no sense.
The controversy on RRT timing will not be solved by unplanned analyses of published trials but by the accumulation of evidence-based from large RCTs.
AKIKI: Key messages

- Delayed RRT initiation strategy **obviated the need for RRT** in almost 50% of cases

- Mortality at day 60 did not **differ** significantly between groups

- **Catheter-related infections:** less frequent with the delayed strategy

- **Renal function recovery:** more rapid with the delayed strategy

- **November 2016:**
  
  *A conservative strategy might be considered as the standard*
Thanks

Patients and their surrogates

Pr Didier DREYFUSS

DSMB
Pr Laurent Brochard
Pr Christian Melot
Pr Alexandre Hertig

Dr David HAJAGE

All study sites investigators, AKIKI Study group