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A Critical Review of Timing of Dialysis Initiation

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Timing of Initiation of Dialysis

“Early Versus Late RRT”

- For AKI
- For ESRD



MAKING
DIALYSIS
SAFER

I don't care what day it is.
Four hours is four hours.

Early Versus Late RRT For AKI

Background

- **There is currently no validated strategy for the timing of renal replacement therapy RRT for AKI in ICU** *when short-term life-threatening metabolic abnormalities are absent.*
- **No adequately powered prospective randomized study** *has addressed this issue to date.*
- **Significant practice heterogeneity exists** *and may expose patients to either unnecessary hazardous procedures or undue delay in RRT.*

Early Versus Late RRT For AKI

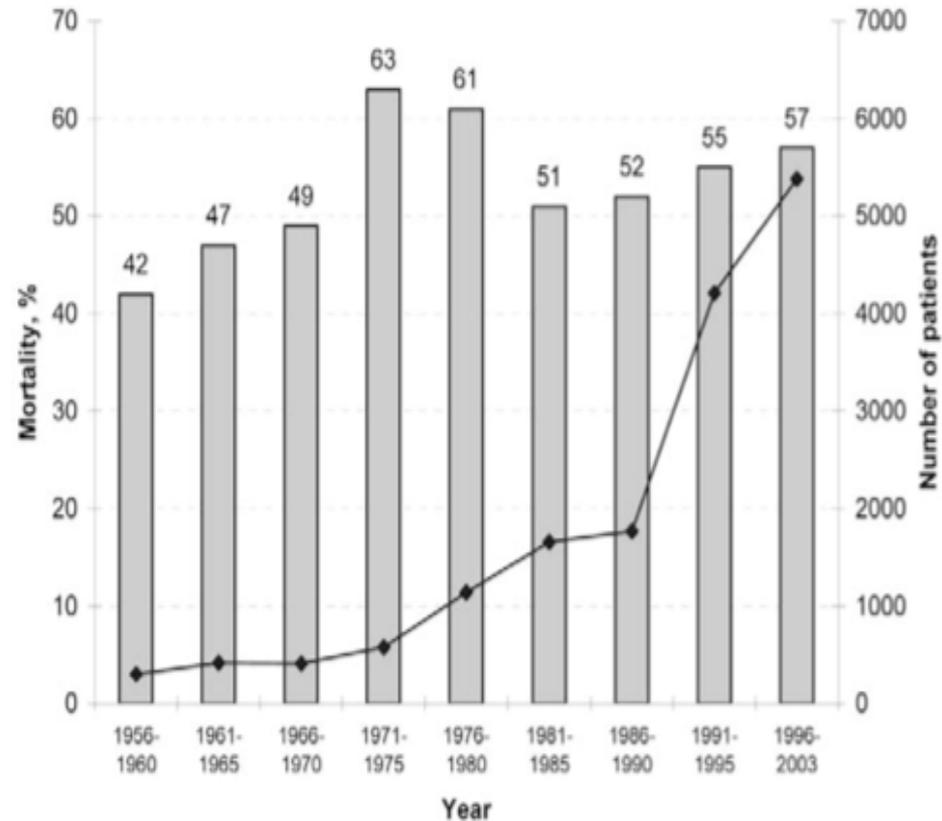
Conceptual facts

- AKI is a medical complication associated with significant morbidity and mortality in critically ill patients.
- AKI is common in critical illness, and severe AKI is associated with up to 60 % hospital mortality.

Shortgen et al., Am J Respir Crit Care Med. 2000;162:197–202.

Uchino et al., JAMA. 2005;294(7):813–8.

Gaudry et al.; licensee BioMed Central. 2015



Early Versus Late RRT For AKI

It seems logical to initiate early dialysis in AKI.

Benefits :

1. *Volume control*
2. *Ease of parenteral nutrition*
3. *Establishing acid-base homeostasis*
3. *Removal of endotoxins and inflammatory mediators*



One size doesn't fit all

Early start on continuous hemodialysis therapy improves survival rate in patients with acute renal failure following coronary bypass surgery

Souichi Sugahara, Hiromichi Suzuki 

First published: 12 October 2004 [Full publication history](#)

- Survival between 14 patients who started to receive dialysis therapy when urine volume decreased to less than 30 mL/hr and another group of 14 patients who waited to begin dialysis therapy until the level of urine volume was less than 20 mL/hr for 14 days following coronary bypass graft surgery.
- **14-day mortality** within the “**early**” group was **14 %** (2 of 14), compared with **86 %** (12 of 14) in the “**late**” group ($p < 0.01$).

Early Versus Late RRT For AKI

- The magnitude of the **mortality benefit** reported in Sugahar's trial associated with "early" RRT has **not been reproduced by subsequent investigators.**



Biomarkers of rapid chronic kidney disease progression in type 2 diabetes
Looker, Helen C. et al.

Comparison of standard and accelerated initiation of renal replacement therapy in acute kidney injury

Ron Wald  , [Neill K.J. Adhikari](#), [Orla M. Smith](#), [Matthew A. Weir](#), [Karen Pope](#), [Ashley Cohen](#), [Kevin Thorpe](#), [Lauralyn McIntyre](#), [Francois Lamontagne](#), [Mark Soth](#), [Margaret Herridge](#), [Stephen Lapinsky](#), [Edward Clark](#), [Amit X. Garg](#), [Swapnil Hiremath](#), [David Klein](#), [C. David Mazer](#), [Robert M.A. Richardson](#), [M. Elizabeth Wilcox](#), [Jan O. Friedrich](#), [Karen E.A. Burns](#), [Sean M. Bagshaw](#) on behalf of the Canadian Critical Care Trials Group

- Patients randomized from a point in time triggered by the development of biochemical renal injury reflected by a RIFLE grade of “failure”, oliguria less than 0.3 ml/kg/h for 12 h, or anuria lasting more than 12 h).

Early Versus Late RRT For AKI

- “Early” group to mean time to RRT of 9.2 h and a “late” RRT group with a mean time to RRT of 32 h after biochemical inclusion criteria were met.
- No significant difference in mortality rates between their two groups ($p = 0.74$).

Wald et al., Kidney Int. 2015;88(4):897–904.

Early Versus Late RRT For AKI

Earlier studies showed that an earlier initiation of dialysis was better in relation to mortality in AKI.

In conclusion

- **Early studies on this topic were small and may have overestimated an effect size associated with “early” RRT based on the small size of the study populations.**

Early Versus Late RRT For AKI

The Current Status

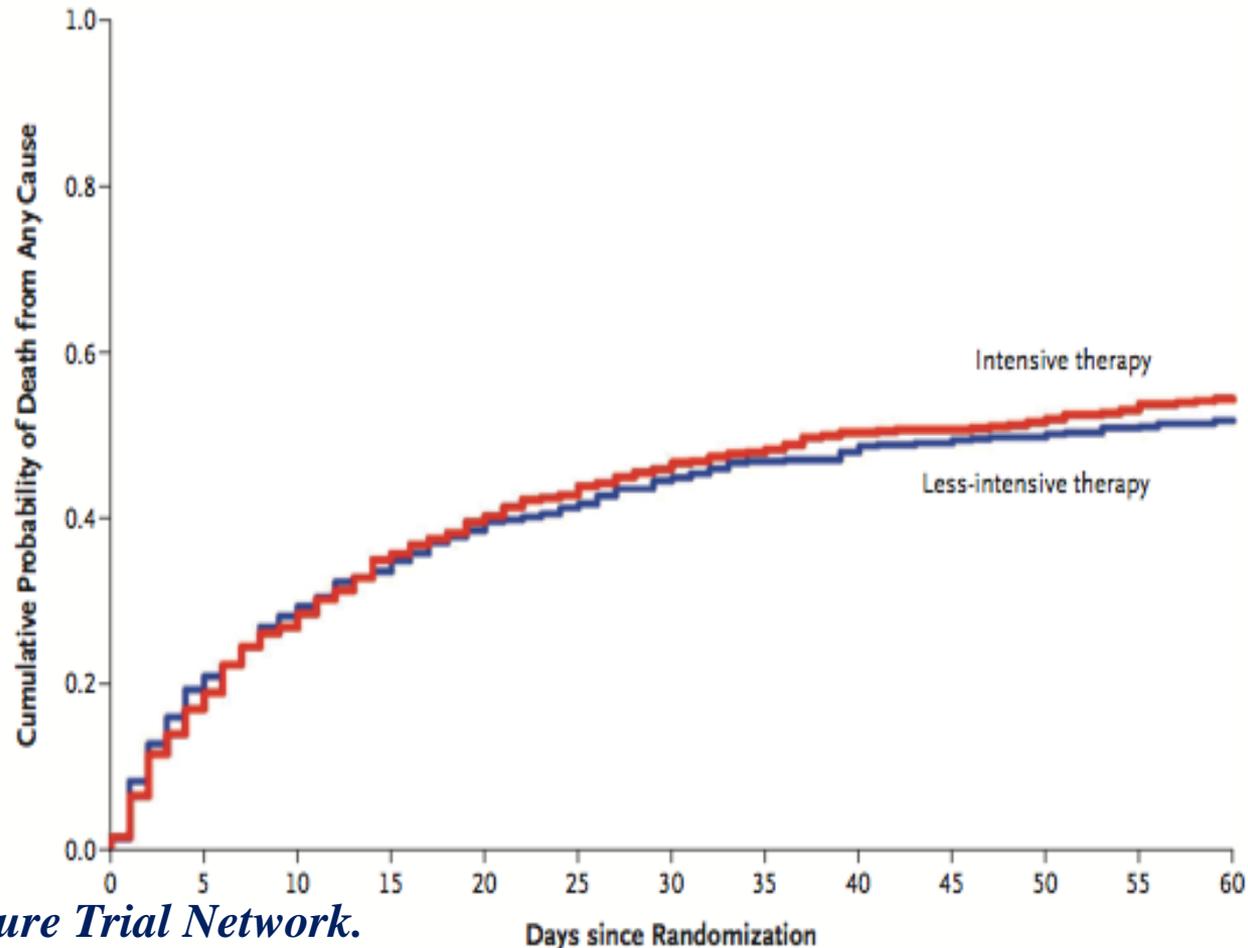
- The optimal timing of RRT in critically ill patients is unknown.
- Despite decades of research and scores of studies mortality in AKI has remained stubbornly elevated.

**Actually, we have no idea
what to do!!!!**



RRT Dose For AKI

- Dialysis dose was the target and higher dose was going to be the key to better outcomes with dialysis dependent AKI.
- This was definitively rejected by The ATN Trial.



*The VA/NIH Acute Renal Failure Trial Network.
N Engl J Med 2008; 359:7-20 July 3, 2008.*

The impact of “early” versus “late” initiation of renal replacement therapy in critical care patients with acute kidney injury: a systematic review and evidence synthesis

Benjamin T. Wierstra, Sameer Kadri, Soha Alomar, Ximena Burbano, Glen W. Barrisford and Raymond L. C. Kao 

Critical Care 2016 20:122 | DOI: 10.1186/s13054-016-1291-8 | © Wierstra et al. 2016

- Despite several studies having been conducted on this topic over the last 30 years, a clear answer regarding the optimal timing of RRT in critical illness remains elusive.

Benjamin et al., Critical Care 2016; 20:122

fresh RCT data on when to initiate dialysis in AKI

AKIKI Trial

The Artificial Kidney Initiation in Kidney Injury

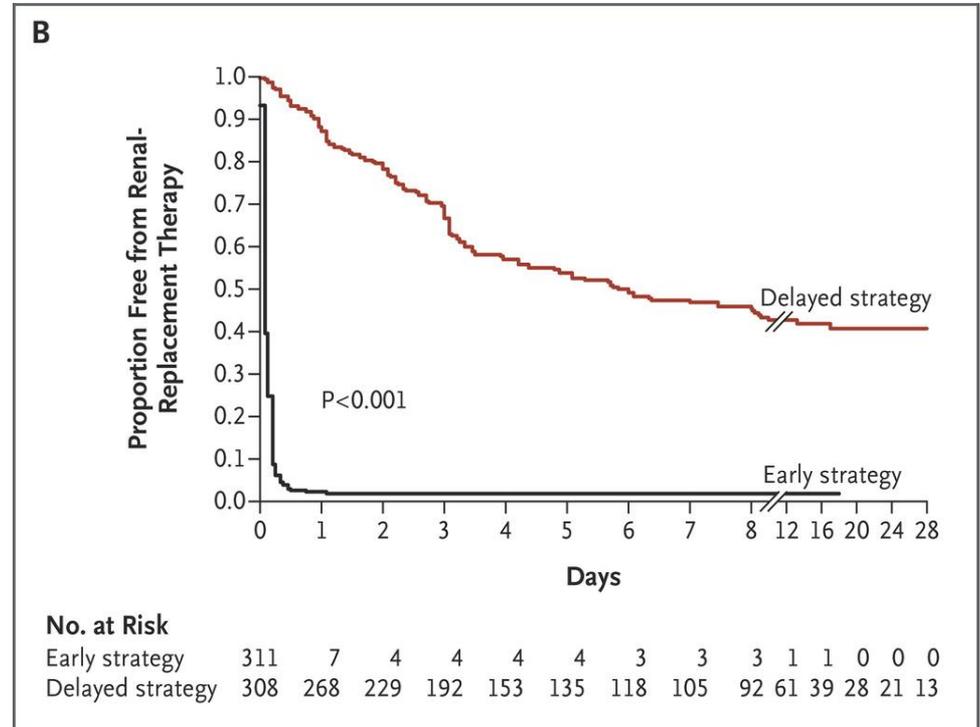
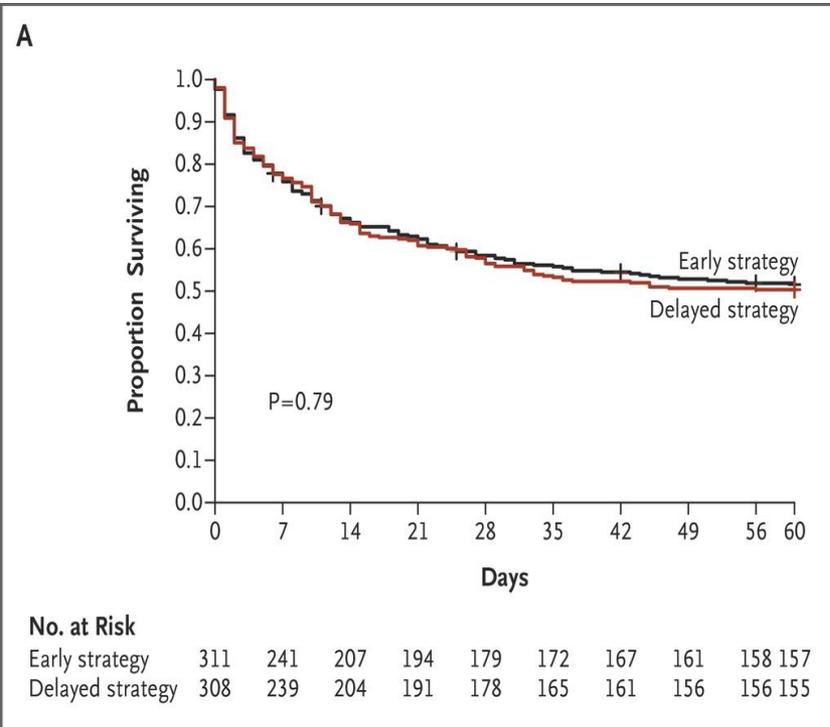
- Two-group randomized trial conducted in 31 intensive care units in France from September 2013 through January 2016.
- **Patients (n=620, power 90%)** admitted to the **ICU** with **AKI** that was compatible with a diagnosis of **ATN** in the context of ischemic or toxic injury and were receiving invasive mechanical ventilation, catecholamine infusion. To undergo randomization patients had KDIGO stage 3 AKI.

(The investigators sought to shed light on this question with an open-label, prospective randomized trial.)



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

Gaudry et al., N Engl J Med 2016; 375:122-133 July 14, 2016.



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 RRT in an appreciable number of patients.

The AKIKI Trial

- Mortality was the same between the two groups.
- There were 303 deaths by 60 days after randomization, 150 in the early initiation cohort, 153 in the late initiation cohort.
- Late dialysis had the same mortality with half as much dialysis as the early start cohort.

The ELAIN Trial

shows advantages of early RRT

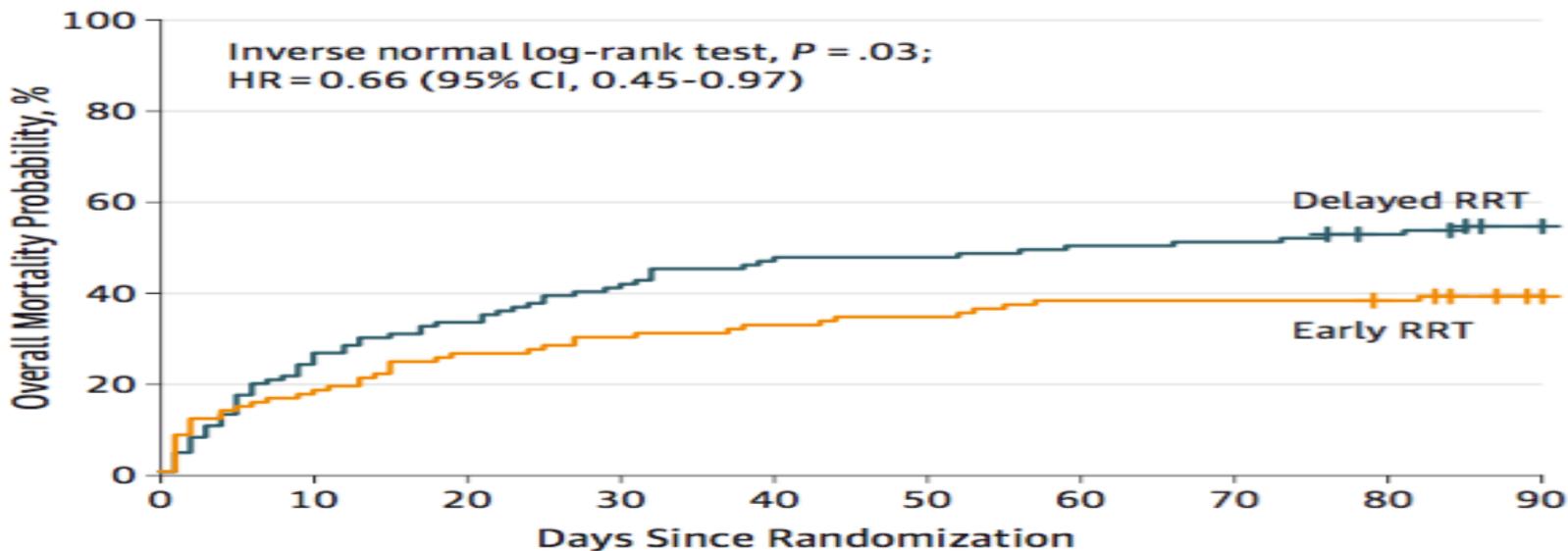
Zarbock et al., JAMA 2016; 315:2190–2199

- Single-center randomized clinical trial of 231 critically ill patients with AKI Kidney Disease: Improving Global Outcomes (KDIGO) stage 2 (≥ 2 times baseline or urinary output < 0.5 mL/kg/h for ≥ 12 hours).
- Plasma neutrophil gelatinase-associated lipocalin **NGAL level higher than 150 ng/mL**.
- Enrolled between August 2013 and June 2015 from a university hospital in Germany.

INTERVENTIONS:

- **Early** (within 8 hours of diagnosis of KDIGO stage 2; $n = 112$) or **delayed** (within 12 hours of stage 3 AKI or no initiation; $n = 119$) initiation of RRT.

Mortality Probability Within 90 Days After Study Enrollment for Patients Receiving Early and Delayed Initiation of Renal Replacement Therapy (RRT)

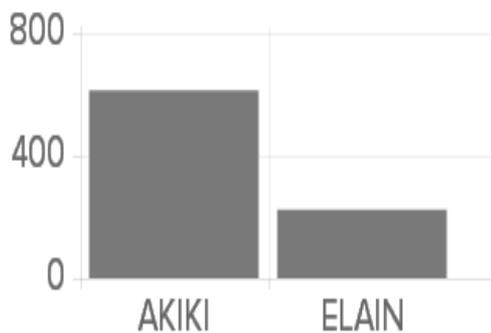


No. at risk										
Early RRT	112	92	82	78	75	73	69	69	66	55
Delayed RRT	119	90	79	70	63	62	59	58	54	48

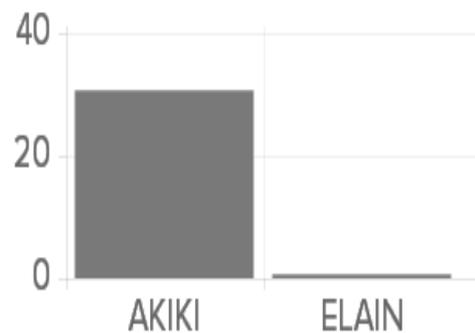
The survival was significantly better with early initiation of dialysis.

ALAIN treated all patients with CRRT

Number of patients



Number of centers



RRT For AKI

Conclusion

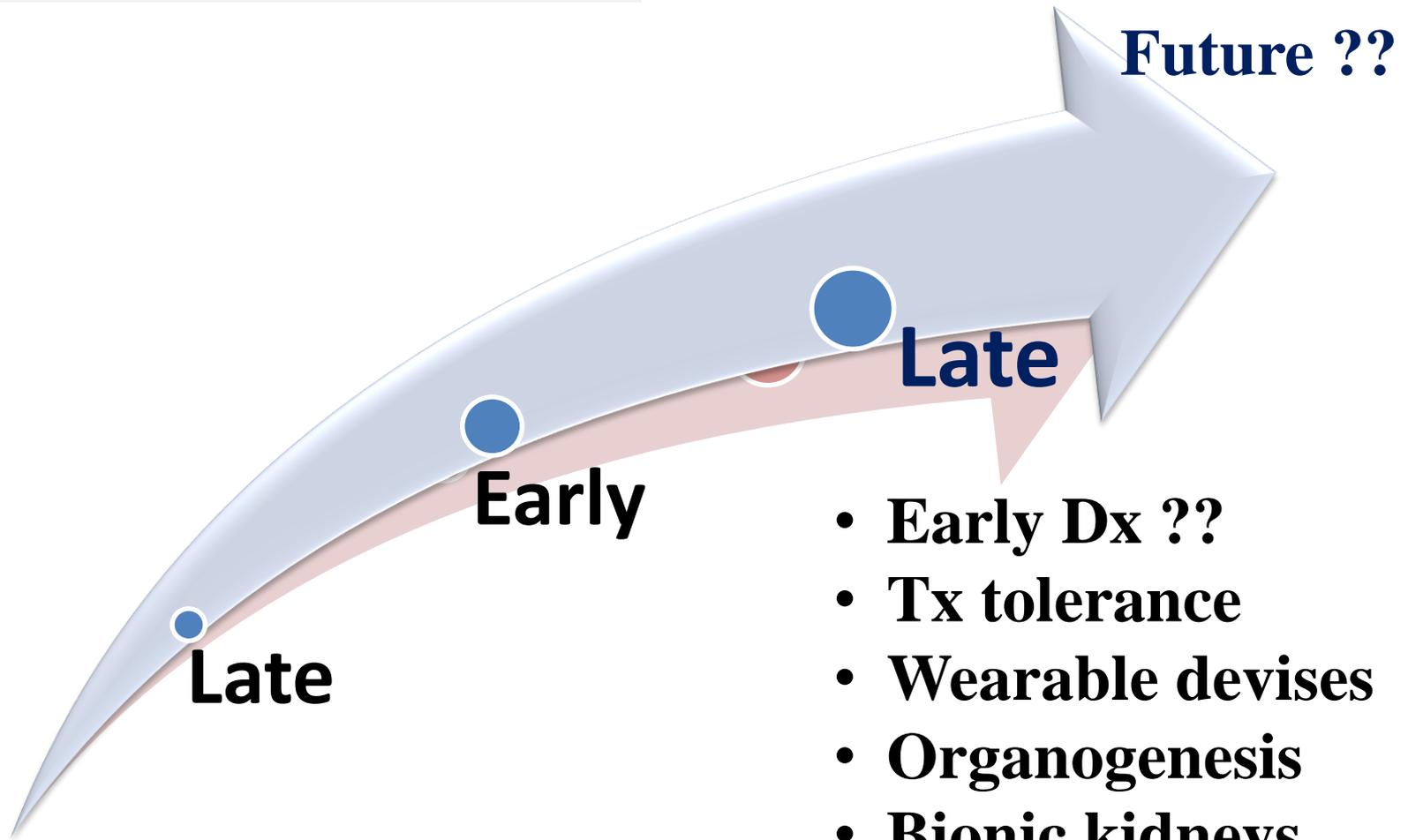
- Earlier initiation of RRT may produce benefits by avoiding hypervolemia, eliminating of toxins, establishing acid-base homeostasis, and preventing other complications attributable to AKI.
- However, early initiation of RRT may unnecessarily expose some patients to potential harm because some patients will spontaneously recover renal function.

Early Versus Late Dialysis for ESRD

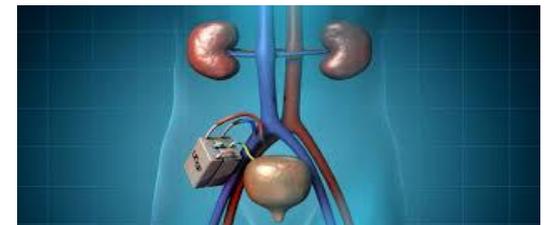
Early Versus Late Initiation of Dialysis for ESRD



Initiating dialysis for ESRD



- **Early Dx ??**
- **Tx tolerance**
- **Wearable devises**
- **Organogenesis**
- **Bionic kidneys**



Early versus Late dialysis for ESRD

- (Total $n = 896,546$). 99,231 patients had an early dialysis start (eGFR >15 ml/min per 1.73 m^2).
- 113,510 had a late start (eGFR ≤ 5 ml/min per 1.73 m^2).



Early versus Late dialysis for ESRD

- This retrospective analysis of the USRDS data suggests that late initiation of dialysis is associated with a reduced risk of mortality.
- Early dialysis initiation based only on eGFR without clinical indications cannot be recommended.

Early Start of Dialysis: A Critical Review

Steven Rosansky*, Richard J. Glassock[†], William F. Clark[‡]

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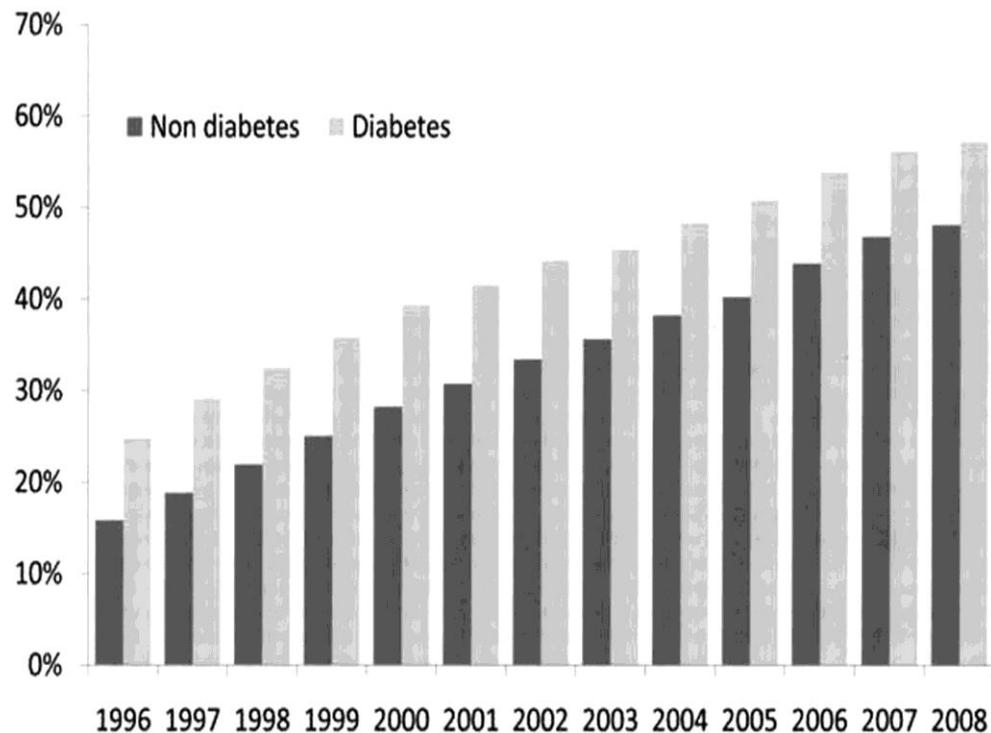
doi: 10.2215/
CJN.09301010
CJASN May 2011 vol. 6 no.
5 1222-1228

Abstract *Free*

» Full Text *Free*

Full Text (PDF) *Free*

**Incident cases with eGFR ≥ 10
Percent of total Incident Cases**



To justify early dialysis treatment, the therapy must provide a morbidity, mortality, or quality of life benefit.

Early Start of Dialysis: A Critical Review ↔

Steven Rosansky^{*}, Richard J. Glassock[†], William F. Clark[‡]

[+](#) Author Affiliations

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This Article

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CJASN May 2011 vol. 6 no.
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Abstract *Free*

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- Hemodialysis may promote non–coronary artery disease–related transient myocardial ischemia; myocardial “stunning”.
- Compared with nondialyzed patients with eGFR <15 ml/min per 1.73 m², dialyzed patients had twice the rate of sudden death



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ORIGINAL ARTICLE

A Randomized, Controlled Trial of Early versus Late Initiation of Dialysis

Bruce A. Cooper, M.B., B.S., Ph.D., Pauline Branley, B.Med., Ph.D., Liliana Bulfone, B.Pharm., M.B.A., John F. Collins, M.B., Ch.B., Jonathan C. Craig, M.B., Ch.B., Ph.D., Margaret B. Fraenkel, B.M., B.S., Ph.D., Anthony Harris, M.A., M.Sc., David W. Johnson, M.B., B.S., Ph.D., Joan Kesselhut, Jing Jing Li, B.Pharm., B.Com., Grant Luxton, M.B., B.S., Andrew Pilmore, B.Sc., David J. Tiller, M.B., B.S., David C. Harris, M.B., B.S., M.D., and Carol A. Pollock, M.B., B.S., Ph.D., for the IDEAL Study^{*}

N Engl J Med 2010; 363:609-619 | August 12, 2010 | DOI: 10.1056/NEJMoa1000552

In this study involving patients with CKD, **early** initiation of dialysis had **no significant effect** on the rate of **death from any cause** or on **CV** events, **infectious** events, or **complications of dialysis**.

The Initiating Dialysis Early and Late (IDEAL) study: study rationale and design.

Cooper BA¹, Branley P, Bulfone L, Collins JF, Craig JC, Dempster J, Fraenkel MB, Harris A, Harris DC, Johnson DW, Kesselhut J, Luxton G, Pilmore A, Pollock CA, Tiller DJ; IDEAL Study Steering Committee.

- The Initiating Dialysis Early And Late (IDEAL) trial provides guidance on the safety of waiting for symptoms or lower levels of estimated glomerular filtration rate prior to beginning dialysis.
- Economic analyses based on the IDEAL and US Renal Data System findings suggest that significant cost savings could be achieved by reversing the early initiation trend.

Early Versus Late Dialysis for ESRD

- Late initiation of dialysis is associated with a reduced risk of mortality, arguing against aggressive early dialysis initiation based primarily on eGFR alone.

Conclusion

- Follow a general outline.
- A tailored decision.
- Judgment based on experience.



*Thank you
for your kind
attention*



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