When to initiate Dialysis?

Is it Really True that the Earlier the Better?

Prof. Francesco Locatelli MD FRCP

Department of Nephrology, Dialysis and Renal Transplant

“Alessandro Manzoni” Hospital – Lecco, Italy
Initiation of dialysis at higher GFRs: is the apparent rising tide of early dialysis harmful or helpful?

 Patients starting dialysis at higher GFRs
Age and comorbidity may explain the paradoxical association of an early dialysis start with poor survival.
Influence of early dialysis among patients with advanced chronic renal disease: results of a systematic review

1,463 REFERENCES (up to February 2009)

HTA 8 papers
DARE 16 papers
COCHRANE 5 papers
PUBMED 450 papers
EMBASE 30 papers
ISI 954 papers

1413 papers excluded

50 papers Perusal of complete text

9 papers MANUAL REVIEW

10 papers included in the Review → All cohort studies 7 retrospective 3 prospective

Influence of early dialysis among patients with advanced chronic renal disease: results of a systematic review

Time of treatment initiation and dialysis modality

- Studies of patients on HD (Kazmi, Wilson), reported a higher mortality with early treatment.

- Studies of patients on PD indicated better survival with early initiation in one case (Tang) and “contradictory” results in the other (Shiao).

- Mixed HD/PD studies in one case (Beddhu) indicated a 1.4-fold rise in the risk of death for every increase of 5 mL/min in eGFR at initiation of treatment, and in the other (Korevaar) a small beneficial effect of early initiation.

Influence of early dialysis among patients with advanced chronic renal disease: results of a systematic review

- The main limitation of these studies is the presence of lead-time bias: an erroneous survival benefit is attributed to the early referral of patients to dialysis, that is, earlier initiation of dialysis prolongs time on dialysis but does not change patient survival.

- No conclusions can be drawn as to the optimal time for initiating RRT as these studies are contradictory and include methodological shortcomings from prospective studies.

Multicenter, randomized, controlled trial

To examine whether the timing of the initiation of maintenance dialysis influenced survival among patients with chronic kidney disease.

Primary outcome: death from any cause.
Study Course

July 2000 – Nov. 2008
GFR 10-15 ml/min

2928 pts were screened

32 Centers in Australia and New Zealand

mean 60.4 years
542 M, 286 F

828 underwent randomization

32 Centers in Australia and New Zealand

(355 diabetes)

Early-Start Group

GFR 10-14 ml/min/1.73 m²
n.
404
10 deaths before dialysis start
383 started dialysis
1.8 months median time to dialysis initiation
(95% CI, 1.60 to 2.23)

Cockroft-Gault

Late-Start Group

GFR 5-7 ml/min/1.73 m²
n.
424
22 deaths before dialysis start
386 started dialysis
7.4 months median time to dialysis initiation
(95% CI, 6.23 to 8.27)

## Results

<table>
<thead>
<tr>
<th></th>
<th>Early-Start</th>
<th>Late-Start</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR (ml/min/1.73 m²) (Cockroft-Gault)</td>
<td>12.0 (18.6%&lt;10)</td>
<td>9.8 (75.9%&gt;7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>MDRD (post-hoc)</td>
<td>9.0</td>
<td>7.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>started HD/PD</td>
<td>n. 383</td>
<td>n. 386</td>
<td></td>
</tr>
<tr>
<td>completed follow-up</td>
<td>134</td>
<td>166</td>
<td></td>
</tr>
<tr>
<td>years of f-up (median, CI)</td>
<td>3.64 (0.03-9.15)</td>
<td>3.57 (0.02-8.78)</td>
<td></td>
</tr>
<tr>
<td>DEATHS</td>
<td>152 (37.6%)</td>
<td>155 (36.6%)</td>
<td>&lt; 0.75</td>
</tr>
</tbody>
</table>

Primary Outcome

Kaplan–Meier Curves for Time to Death

Hazard ratio, 1.04 (95% CI, 0.83–1.30)
P = 0.75

No. at Risk
Early start 404 358 305 249 177 99 59 32
Late start 424 385 333 254 187 115 60 32

A randomized, controlled trial of early versus late initiation of dialysis

Conclusions of the Authors

- Early initiation of dialysis, which has enormous implications in terms of cost and organization, had no significant effect on clinical outcomes (rate of death from any cause, cardiovascular or infectious events or complications of dialysis).

- Dialysis should not be started on the basis of an estimate of GFR alone. With careful clinical management of CKD, dialysis can be delayed for some patients until GFR drops below 70 ml/min or until more traditional clinical indicators for HD initiation are present.
A randomized, controlled trial of early versus late initiation of dialysis

Acknowledged Study Limitations

- **Use of eGFR based on the Cockcroft–Gault equation.**
  MDRD equations were not widely used when the trial was designed and had not been validated in patients with low levels of renal function.

- **Lack of the use of a uniform method of creatinine assessment.**
  Pitfalls related to creatinine level variability with sex, race, mass, etc. Likely to have been mitigated by patients stratification according to the study center.

- **Mean eGFR difference of only 2.2 ml/min between the two groups.**
  ... its effect was an important difference of 6 months between groups in the start time for HD, reflecting the importance of close clinical follow-up in these patients.
The initiation of Renal-Replacement Therapy — Just-in-time delivery
Lameire N and Van Biesen W

- Do the results of the IDEAL trial imply that the initiation of dialysis can be delayed until an estimated GFR of 5 to 7 ml/min x 1.73 m² is reached?

Clinical symptoms and patient follow up are of greater importance than eGFR

- A mean difference between the groups of 2.2 ml/min x 1.73 m² in eGFR, is clinically relevant, in view of the inaccuracy of eGFR in this low range.

Starting RRT on the basis of predefined eGFR does not improve the outcome

- The important conclusion of the study is that waiting to initiate dialysis until signs of uremia appear does not jeopardize the patient and that starting RRT on the basis of a predefined eGFR does not improve the outcome.
The main conclusion of this important study— that for asymptomatic patients RRT can be delayed by an average of 6 months— should be placed in perspective.

An important prerequisite for a “wait and see” policy is careful clinical follow-up of each patient. The study protocol explicitly advocated that the method of dialysis be selected, and a functioning peritoneal or vascular access be prepared in advance, a policy that permits the immediate initiation of dialysis if the patient becomes symptomatic.

Early referral, patient-education program and planning before dialysis are the cornerstones of such a strategy.
The patients were relatively healthy

No clear criteria for diagnosis of “uremia”

The Authors have not provided data on urinary output

The IDEAL study is not representative of CKD patients in US and UK
Lessons learnt from the IDEAL study

- No benefit from “early-dialysis”
- Conservative therapy is possible also till GFR <10 ml/min (corresponding to 6 months dialysis delay)
- Importance of close clinical follow up in non-dialysis CKD stage 5 patients
- Pay more attention to patient symptoms than to eGFR
- Importance of nutritional status assessment
- Data from 24 hour urine collection (urea, sodium) are mandatory
- It is possible to safely reduce economic burden due to earlier dialysis

Locatelli F et al. Contrib Nephrol 2011
Dialysis beginning according to international guidelines and clinical data

- Malnutrition
- Metabolic disturbance

**eGFR (ml/min/1.73 m²)**
- 15
- 10 – 8
- 10 – 6
- 6

- K/DOQI 2006
- EBPG 2005 and ERBP 2011
- Theoretical lower eGFR limit

- Uremic signs and symptoms
- Fluid overload diuretic-refractory

Locatelli F et al. Contrib Nephrol 2011
Lessons from recent trials in hemodialysis

The IDEAL study: what can we learn?

- Even if with some limitations, the IDEAL study represents a very important trial. Its main message is the lack of a fixed GFR value at which to start dialysis in asymptomatic patients, suggesting to give more relevance to close patient monitoring (uremic signs and symptoms, fluid overload, malnutrition, etc.)

- This approach has been proven to be safe for the patients and effective in temporary delaying the need for dialysis
When to start dialysis: Updated guidance following publication of the Initiating Dialysis Early and Late (IDEAL) study

James Tattersall, Friedo Dekker, Olof Heimbürger, Kitty Jager, Norbert Lameire, Elizabeth Lindley, Wim Van Biesen, Raymond Vanholder, Carmine Zoccali on behalf of the ERBP Advisory board.

**Updated guidance**

The 2002 guidance is not significantly changed. The evidence levels are increased by the studies published since 2002. The caution against using creatinine and CC to guide dialysis start is strengthened. A caution that eGFR calculated by the MDRD method is not useful in determining need for dialysis has been added. The emphasis on using GFR of 6 ml/min/1.73m² as an absolute lower limit to starting dialysis is made more vague. Support for establishing advanced CKD clinics has been added.

Nephrol Dial Transplant 2011,
KWGO Controversies Conference

Novel techniques and innovation in blood purification: How can we improve clinical outcomes in hemodialysis?

14-15 October, 2011
Paris, France

CONFERENCE LEADERS

Christopher T Chan, MD – Conf. Co-Chair
University of Toronto
Toronto, CANADA
Christopher.Chan@uhn.on.ca

Nathan Levin, MD – Conf. Co-Chair
Renal Research Institute
New York, NY, UNITED STATES
nlevin@rriny.com

Francesco Locatelli, MD – Conf Co-Chair
Alessandro Manzoni Hospital
Lecco, ITALY
f.locatelli@ospedale.lecco.it

Bertram Kasiske, KDIGO Co-Chair
Hennepin County Medical Center
Minneapolis, MN, UNITED STATES
kasis001@umn.edu

Kai-Uwe Eckardt, MD – KDIGO Co-Chair
University Hospital Erlangen
Erlangen, GERMANY
Kai-Uwe.Eckardt@uk-erlangen.de
Lessons from recent trials in hemodialysis

- Randomised controlled studies in dialysis are welcomed
- The HEMO, MPO, Italian Convective Study and the Contrast, the Turkish and Catalanian studies, comparing hemodialysis, hemodiafiltration and hemofiltration trials gave important information on how to improve the management of dialysis patients
- The IDEAL and the FHN Daily Trial are well designed randomized controlled trials aimed at improving the everyday quality of dialysis treatment