Early Start of Hemodialysis May Be Harmful

Steven J. Rosansky, MD; Paul Eggers, PhD; Kirby Jackson, BA; Richard Glassock, MD; William F. Clark, MD

Background: A dramatic increase in the “early start” of dialysis with an estimated glomerular filtration rate (eGFR) at least 10 mL/min/1.73 m² has occurred in the United States since at least 1996. Several recent studies have reported a comorbidity-adjusted survival disadvantage of early start of dialysis. The current study examines a relatively “healthy” dialysis cohort to minimize confounding issues and determine whether early initiation of hemodialysis is associated with a survival benefit or harm.

Methods: We examined demographics, year of dialysis initiation, primary etiology of renal failure, and body mass index, hemoglobin, and serum albumin levels in 81,176 nondiabetic, 20- to 64-year-old, in-center incident hemodialysis patients with no reported comorbidity besides hypertension. We compared survival, using a piecewise proportional hazards model to estimate covariate-adjusted mortality hazard ratios (HRs) for eGFR at the time of initiation of dialysis. We also performed time-dependent adjusted analysis stratified by initial serum albumin levels lower than 2.5 g/dL, 2.5 to 3.49 g/dL, and 3.5 g/dL or higher (the “healthiest” group [HG]).

Results: Unadjusted 1-year mortality by eGFR ranged from 6.8% in the reference group (eGFR <5.0 mL/min/1.73 m²) to 20.1% in the highest eGFR group (≥15.0 mL/min/1.73 m²). Compared with the reference group, the HR for the HG was 1.27 (eGFR, 5.0-9.9 mL/min/1.73 m²), 1.53 (eGFR, 10.0-14.9 mL/min/1.73 m²), and 2.18 (eGFR ≥15.0 mL/min/1.73 m²) and ranged from 1.50 to 3.53 mL/min/1.73 m² in the first year of dialysis for the early-start group.

Conclusion: The increased HR during hemodialysis associated with early start in the healthiest group of patients undergoing dialysis indicates that early start of dialysis may be harmful.


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The initiation of hemodialysis therapy in a patient with advanced renal failure should lead to a decrease in expected mortality or morbidity and improved quality of life relative to nonhemodialytic therapy (both including frequent monitoring of clinical signs and laboratory data). An adverse effect of hemodialytic therapy on the quality of life in frail elderly patients has been recently described.1 The appropriate timing for initiating hemodialysis relative to estimated levels of residual renal function is an important, but as yet unresolved, question having considerable patient outcome and financial consequences.2,3

We recently reported on a trend to “early start” of hemodialysis in the United States.3 Early start was defined as the commencement of regular hemodialysis treatment of end-stage renal disease (ESRD) when the estimated glomerular filtration rate (eGFR) was at least 10 mL/min/1.73 m². Most of the increase in the incident population undergoing hemodialysis from 1996 to 2006 was accounted for by patients meeting this early start definition.3

Since 2002, 9 studies, including our own, have reported a survival disadvantage with higher eGFR at initiation of hemodialysis.5-11 With 1 exception,9 these reports demonstrated that age and comorbidity adjustments attenuated, but did not entirely eliminate, the survival advantage of early start of hemodialysis therapy. In a recently published study from Taiwan,10 a comorbidity-adjusted, inverse relationship between eGFR at initiation of hemodialysis and subsequent survival was reported in a population with a median eGFR of 4.7 mL/min/1.73 m². The recently published randomized controlled trial Initiating Dialysis Early and Late (IDEAL)12 found no survival benefit of early hemodialysis initiation. The small

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separation of initial eGFR for the early- and late-start groups may have eliminated the possibility of demonstrating a survival disadvantage of early hemodialysis initiation.

To try to reduce potential bias of prior observational studies, we selected a cohort with the following characteristics: age 20 to 64 years, without diabetes mellitus (DM), who initiated hemodialysis during the 1996-2006 interval, were included in the US Renal Data System (USRDS), and who had no reported comorbidities other than hypertension. We postulated that this “healthy” cohort with low comorbidity would reduce or eliminate much of the selection biases and lessen the need for multiple adjustments for comorbid conditions that confounded earlier observational studies. Serum albumin level is an important comorbidity factor. Thus, we replicated the main analyses on a healthier subset of patients with serum albumin levels of 3.5 g/dL or higher prior to hemodialysis initiation (the healthiest group, hereinafter HG) (to convert serum albumin to grams per liter, multiply by 10). We hypothesized that if hemodialysis provided a benefit or harm on a healthier subset of patients with serum albumin 

DATA SOURCES AND STUDY POPULATION

Patient information was obtained from the ESRD medical evidence form (form 2728) used to enroll patients in the Center for Medicare and Medicaid Services (CMS) Medicare program. The form contains information on patient’s age; sex; race/ethnicity; primary cause of renal failure; height; weight; and serum levels of creatinine, albumin, and hemoglobin. The form also contains information on comorbidities such as DM, congestive heart failure, hypertension, atherosclerotic heart disease, peripheral vascular disease, current tobacco use, alcohol or drug dependency, and inability to ambulate or transfer.

We examined the ESRD incident population from 1996 through 2006 with first treatment modality of in-center hemodialysis. Exclusion criteria included age younger than 20 years or older than 64 years, DM as a cause of ESRD, and any reported comorbidity other than hypertension. We included persons with hypertension as a comorbid factor because of its high prevalence and because it had little or no effect on mortality adjustments. This resulted in a study population of 120,685 patients (Table 1). The subpopulation with any comorbidity was analyzed separately to examine the effect of comorbidity on survival in this relatively healthy cohort.

COVARIATES

Covariates included age, sex, race/ethnicity, primary etiology of renal failure, year of treatment, hemoglobin (milligrams per deciliter level, serum albumin level (grams per deciliter), and body mass index (BMI), calculated as weight in kilograms divided by height in meters squared.

Serum creatinine level was used to calculate eGFR by the 4-variable modification of diet in renal disease (MDRD) study equation: eGFR (mL/min/1.73 m²) = [186 × serum creatinine × age × 0.742 (if female) × 1.21 (if black) × 0.742 (if female)]. (To convert serum creatinine to micromoles per liter, multiply by 88.4.)

The following measures taken at the initiation of hemodialysis were reported. Four eGFR strata were used: 0 to 4.9 mL/min/1.73 m² (reference group), 5.0 to 9.9 mL/min/1.73 m², 10.0 to 14.9 mL/min/1.73 m², and 15 mL/min/1.73 m² or higher. The age ranges were 20 to 44 years, 45 to 54 years, 55 to 64 years, and 65 years or older. The other measures were sex, race, primary etiology of renal failure (hypertension; polycystic kidney disease [PKD]; other urologic cause of renal failure, other cause, or unknown cause; year of hemodialysis initiation [1996-1999, 2000-2003, 2004-2006]; and serum albumin level [3 albumin strata were used: <2.5 g/dL, 2.5-2.49 g/dL, and ≥3.5 g/dL (reference group])}

STATISTICAL ANALYSIS

Patient survival was calculated from the start of hemodialysis until death with censoring for transplantation and date of last follow-up (the end of follow-up was August 31, 2007). Unadjusted survival by 3 albumin and 4 eGFR groups was calculated at 1 and 2 years after hemodialysis initiation. Mortality hazard models used the following reference groups: the group with eGFR of 0 to 4.9 mL/min/1.73 m² (late-start group); those who were white; females; whose primary etiology was hypertension; those with a BMI of 25 to 29; and groups with serum albumin level of 3.5 g/dL or higher. Incident year and hemoglobin levels were treated as continuous variables.

Significance tests for homogeneity of variables were calculated using χ² tests for categorical variables and t test for continuous variables. A standard Cox proportional hazards model with covariate adjustment comprised the main analysis. In addition, an extended Cox hazards model allowing piecewise nonproportionality for eGFR and albumin level category with change points at 6 months, 12 months, and 24 months was used to determine the time-dependent effect of eGFR and serum albumin on mortality. Other variables were modeled assuming proportionality. More general models that did allow nonproportionality of other variables were examined, which did not change the results. A separate model was also examined for the highest serum albumin level (≥3.5 g/dL). This modeling allows for different effect of each covariate for HGs. All analyses were conducted using SAS statistical software (version 9.2; SAS Inc, Cary, North Carolina).

CHARACTERISTICS OF THE STUDY COHORT

From 1996 through 2006, the total population undergoing incident hemodialysis was 1,009,381, of whom 505,338 were 20 to 64 years old (Table 1). Of this group, 228,981 did not have DM as a reported primary etiology of renal disease or any reported comorbidity, and 180,845 of these incident patients were treated with hemodialysis. Excepting hypertension as a reported comorbidity, 60,160 had 1 or more comorbidities, leaving 120,685 patients. Of these patients, 39,509 were eliminated owing to missing information (4% were missing data for BMI, 11% were missing data for hemoglobin level, 19% were missing data for serum albumin level, and 6% were missing other data), resulting in a final low comorbidity study cohort of 81,176 patients. In the 60,160 patients with reported comorbidity (excluded from the study cohort), the age-adjusted mortality rate varied from 1.4 to 1.7 for the comorbidities current smoking and chronic obstructive pulmonary disease, respectively, and 1.8 to 2.5 for drug dependence and in-
The frequency of early start (eGFR $\geq 15$ mL/min/1.73 m$^2$) increased with age (55-64 years vs 20-44 years) and was more common in males than in females and in black patients compared with white patients ($P < .001$). Early start of hemodialysis was less frequent in adults with PCKD and glomerulonephritis ($P < .001$). Of the total early-start cohort, over half began hemodialysis in the 2003-2006 interval vs the 1996-2002 interval. The BMI and serum albumin levels were lower, while hemoglobin levels were higher in the early-start cohort vs the late-start cohort. Serum albumin levels lower than 2.5 g/dL were more frequent in the late-start cohort ($P < .001$).

Table 2 shows that the first-year mortality in the study cohort was 9.4%, dropping to 7.1% in the second year. Mortality was 3 times greater (20.1%) in the early-start group compared with the late-start group (6.8%). Similarly, persons with the lowest albumin level were 5 times as likely to die in the first year (21.0%) as those with the highest albumin level (4.7%). The direct relationship between higher initial eGFR and first-year mortality was evident within all albumin levels, but the HG demonstrated the highest relative effects (3.5-fold greater mortality with an eGFR of 15 mL/min/1.73 m$^2$ or higher vs lower than 5 mL/min/1.73 m$^2$).

UNADJUSTED AND ADJUSTED MORTALITY HAZARD RATIOS

Table 3 shows the unadjusted and fully adjusted (for all covariates in the table) mortality hazard ratios (HRs) for the overall population and the HG (albumin level $\geq 3.5$ g/dL). For the overall study population, increasing age,
male sex, black race, and a BMI lower than 25.0 had a negative effect on survival, whereas higher levels of hemoglobin, later year of treatment, Asian race, and primary etiology of PCKD or glomerular disease had a positive effect on survival (P < .001 for all comparisons). These effects were similar in the HG except for a survival advantage for black race. Adjusted HRs for the overall population by the 3 eGFR groups, relative to the reference group, were 1.23, 1.47, and 1.74, respectively, and for the HG were 1.27, 1.53, and 2.18, respectively.

We determined that both eGFR and serum albumin level had time-dependent effects on mortality (Figure). The effect of early start was not as evident in the group with low albumin level (Figure, A). The HR for persons with an eGFR of 5.0 to 9.9 mL/min/1.73 m² did not change greatly over time for all albumin-level groups. In the HG group, the association of early start and poor relative survival is seen in the cohort with an eGFR of 15 mL/min/1.73 m² or higher; the HR was 3.53 in the first 6 months and declined to 1.57 after 2 years.

As shown in prior studies, the presence of reported comorbidity is strongly associated with lower survival. Lassalle et al found that only the patients with the highest comorbidity were at greater risk of death with early hemodialysis. Several large observational studies showed a “dose-response” relationship between comorbidity levels and earlier hemodialysis initiation. In our relatively young cohort without DM, reporting of any comorbid condition doubled the 1-year mortality rate.

In this cohort, overall 1-year mortality was 9.4% compared with 23.8% for the entire USRDS population. Within this cohort, both eGFR and serum albumin level had strong effects on mortality (Table 2). Furthermore, the effect of eGFR on mortality was evident within each albumin level category, and the effect was greatest within the highest albumin category (HG data in Table 2 and Table 3 and Figure, C).

In contrast to our initial hypothesis, the HG showed a relatively greater effect of early-start hemodialysis than the lower albumin level groups (Figure). Kazmi et al also found a higher relative mortality HR in their low-risk cohort. In the current HG, a worse relative survival trend may relate to fewer competing factors for mortality in healthier patients with lower comorbidity who underwent hemodialysis. Patients with high comorbidity and low serum albumin levels (<2.5 g/dL) may have had a greater risk of death independent of hemodialysis. Conversely, those in the HG with lower comorbidity and with higher eGFR at initiation of hemodialysis might have been more susceptible to potential harm from the hemodialysis procedure.

In the study by Beddhu et al, approximately 1000 of the 4000 patients had 24-hour urine creatinine clearance data available. No increase in adjusted HR with early start was found when endogenous creatinine clearance values were used as a measure of residual renal function. Patients undergoing hemodialysis who had higher average serum creatinine levels at initiation of hemod-

### Table 2. First- and Second-Year Mortality for Incident Population of Patients Undergoing Hemodialysis, 1996-2006, Ages 20 to 64 Years, Without DM and With No Other Reported Comorbidity Except Hypertension

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients, No.</th>
<th>Year, Percentage of Patients</th>
</tr>
</thead>
<tbody>
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<td>All persons, %</td>
<td>81 176</td>
<td>9.4</td>
</tr>
<tr>
<td>eGFR&lt;5.0</td>
<td>2.5-3.4 g/dL</td>
<td>10 113</td>
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<td>2.5-3.4 g/dL</td>
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<td>2.5-3.4 g/dL</td>
<td>941</td>
</tr>
<tr>
<td>eGFR&lt;5.0</td>
<td>2.5-3.4 g/dL</td>
<td>19 846</td>
</tr>
<tr>
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<td>2.5-3.4 g/dL</td>
<td>17 308</td>
</tr>
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<td>2.5-3.4 g/dL</td>
<td>941</td>
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Abbreviations: DM, diabetes mellitus; eGFR, estimated glomerular filtration rate.

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As well, if lead time bias is considered, the results pre-
short with an initial eGFR of 5.0 mL/min/1.73 m² or higher.

say type were disproportionately higher in any of the 3 co-
comorbidity serum albumin assay types or creatinine as-
However, there is little reason to suspect that unreported
albumin and creatinine measure methods are unknown.
tate the severity of the comorbidities if present. Also, serum
comorbidity cohort may have had unreported comorbidi-
our study were 0.59 and 0.95, respectively. Thus, our low-
patient sample, reported that the sensitivity and specific-
PCKD, polycystic kidney disease.

mL/min/1.73 m² or higher may be supporting evidence
well as drops in blood pressure during hemodialysis.18

cause of renal failure, hypertension; eGFR, 0 to 4.9; albumin level of 3.5 g/dL or higher; and BMI, 25.0 to 29.9.

SI conversion factor: To convert serum albumin to grams per liter, multiply by 10.

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DM, diabetes mellitus; NA, not applicable; PCKD, polycystic kidney disease.

Table 3. Cox Hazards Models of Mortality: Unadjusted and Adjusted Hazard Ratios (HRs)

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<tr>
<th>Variable</th>
<th>All Persons (n=81 176) Unadjusted HR</th>
<th>P Value</th>
<th>Adjusted HR</th>
<th>P Value</th>
<th>Persons With Albumin Level ≥3.3 g/dL (n=35 665) Unadjusted HR</th>
<th>P Value</th>
<th>Adjusted HR</th>
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cohort. Interpretation of time-dependent individual effects are often difficult in survival models and may be bi-
ased by unobserved covariates. The relative homogeneity of the large study population with low comorbidity and the ability to model survival with many variables adds to the strength of the analysis.13

Although every effort was made to eliminate the effect of comorbid conditions, unmeasured comorbidity could still exist. Longnecker et al.,17 using a 1995-1998 USRDS patient sample, reported that the sensitivity and specificity of the comorbidity data on the CMS 2728 form used in our study were 0.59 and 0.95, respectively. Thus, our low-
comorbidity cohort may have had unreported comorbidities. Furthermore, the CMS 2728 form does not quanti-
tate the severity of the comorbidities if present. Also, serum albumin and creatinine measure methods are unknown. However, there is little reason to suspect that unreported comorbidity serum albumin assay types or creatinine assay type were disproportionately higher in any of the 3 co-
horts with an initial eGFR of 5.0 mL/min/1.73 m² or higher. As well, if lead time bias is considered, the results pre-

The higher relative-first-year hemodialysis mortality rate (Figure) observed for the group with an eGFR of 10 

mL/min/1.73 m² or higher may be supporting evidence for a greater representation of hardy survivors (survivor
bias) who, over time, would die if hemodialysis initiation was delayed. The decreasing HR in the cohort with
albumin level of 2.5 g/dL or higher and eGFR of 10 mL/min/1.73 m² or higher (Figure, B and C) may relate to this
issue. Nevertheless, the 47% to 57% higher HR at 2 years for the group with an albumin level of 3.5 g/dL or higher (Figure, C) makes survivor bias a less likely explanation for our results.

The higher relative hemodialysis mortality rate (Figure) observed in the first year of hemodialysis, especially in patients with a starting eGFR of 10 mL/min/1.73 m² or higher and an initial serum albumin concentration of 3.5 g/dL or higher, raises a concern that hemodialysis may be providing more harm than benefit. Possible mecha-
nisms might include recurrent episodes of myocardial isch-
emia and “stunning” and eventual functional and struc-
tural changes with fixed systolic dysfunction induced by
contventional thrice-weekly hemodialysis.18 In addition,
the risk of sudden cardiac death may double when pa-
patients undergoing hemodialysis.19 Subclinical myocardial ischemia relates directly to ultrafiltration volume as well as drops in blood pressure during hemodialysis.18
Patients undergoing peritoneal dialysis do not exhibit the same degree of myocardial stunning as those undergoing hemodialysis. This may explain the finding by Wright et al that the HR of first-year mortality was significantly higher for patients who underwent early-start hemodialysis vs those undergoing peritoneal dialysis. This hemodynamic disadvantage of hemodialysis was reported by Jansen et al. In the first 3 months of hemodialysis, 27% of the 279 patients in the study exhibited clinically significant hypotension, whereas only 5% of the 243 patients undergoing peritoneal dialysis had clinically evident dehydration in this time interval.

Endogenous renal function in contrast to hemodialytic clearance has been shown to provide a survival benefit. Over 50% of this endogenous renal function may be lost in the first 5 months of hemodialysis treatment. Initiation of hemodialysis owing to inadequate dietary protein intake and declining nutritional
status has not been proven to be efficacious and may even stimulate the inflammation malnutrition syndrome.22

Early start of hemodialysis may be used in an effort to alleviate symptoms related to comorbidities often associated with ESRD.23 These symptoms are frequently nonspecific, including fatigue, anorexia, nausea, and correlate with a low serum albumin level. Whether uses of these indications to initiate hemodialysis are associated with improved survival is unknown.

In conclusion, according to USRDS data, between 1996 and 2008 the fraction of patients initiating hemodialysis with an eGFR higher than 10 mL/min/1.73 m² increased from 20% to 52% and the fraction of those with a starting eGFR of 15 mL/min/1.73 m² or higher increased from 4% to 17% of the incident hemodialysis population.24 This trend has occurred despite no substantial evidence of benefit of early initiation of hemodialysis and many recent publications suggesting potential harm. Hemodialysis is an invasive, lifelong, potentially dangerous intervention. The randomized controlled IDEAL study22 found no benefit of early start of hemodialysis with an MDRD study equation–calculated eGFR level of 7.2 mL/min/1.73 m² in the early-start group vs a level of 2 mL/min/1.73 m² in the early-start group. The failure to find benefit of early hemodialysis by the IDEAL study and the potential harm of early initiation of hemodialysis reported in recent studies and the current observational study provide evidence questioning the trend to early start of hemodialysis. Initiation of hemodialysis should not be based on an arbitrary level of eGFR or serum creatinine level unless this measure is accompanied by definitive end-stage renal failure–related indications for hemodialysis.

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REFERENCES


Correction

Error in Figure. In the Original Investigation titled “The Comparative Safety of Analgesics in Older Adults With Arthritis” by Solomon et al, published in the December 13/27 issue of the Archives (2010;170[22]:1968-1978), an error occurred in the Figure on page 1973. In the graph shown in panel A, the colors of the blue and red lines should have been reversed: the top line should have been red, representing the cumulative event rate of opioids, and the bottom line should have been blue, representing the cumulative event rate of nsNSAIDs (nonselective nonsteroidal anti-inflammatory drugs). The article was corrected online.