Trends in the Timing and Clinical Context of Maintenance Dialysis Initiation

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ABSTRACT
Whether secular trends in eGFR at dialysis initiation reflect changes in clinical presentation over time is unknown. We reviewed the medical records of a random sample of patients who initiated maintenance dialysis in the Department of Veterans Affairs (VA) in fiscal years 2000–2009 (n=1691) to characterize trends in clinical presentation in relation to eGFR at initiation. Between fiscal years 2000–2004 and 2005–2009, mean eGFR at initiation increased from 9.8±5.8 to 11.0±5.5 ml/min per 1.73 m² (P<0.001), the percentage of patients with an eGFR of 10–15 ml/min per 1.73 m² increased from 23.4% to 29.9% (P=0.002), and the percentage of patients with an eGFR>15 ml/min per 1.73 m² increased from 12.1% to 16.3% (P=0.01). The proportion of patients who were acutely ill at the time of initiation and the proportion of patients for whom the decision to initiate dialysis was based only on level of kidney function did not change over time. Frequencies of documented clinical signs and/or symptoms were similar during both time periods. The adjusted odds of initiating dialysis at an eGFR of 10–15 or >15 ml/min per 1.73 m² (versus <10 ml/min per 1.73 m²) during the later versus earlier time period were 1.43 (95% confidence interval [95% CI], 1.13 to 1.81) and 1.46 (95% CI, 1.09 to 1.97), respectively. In conclusion, trends in eGFR at dialysis initiation at VA medical centers do not seem to reflect changes in the clinical context in which dialysis is initiated.


For more than a decade, there has been a pervasive upward trend in the level of eGFR at initiation of maintenance dialysis both within and outside the United States.1–5 The driving forces behind this trend are not well understood. One hypothesis is that trends in eGFR at initiation may signal greater reliance on eGFR versus clinical signs and/or symptoms in deciding when to initiate dialysis.1 Some studies have suggested that changes in the guideline-recommended approach to CKD in the early 2000s—including methods for assessing the severity of CKD and automated reporting of eGFR—may have inadvertently encouraged earlier dialysis initiation in asymptomatic patients based only on their level of eGFR.1,3,6,7 Arguing against this possibility, a recent Canadian study found no evidence that widespread eGFR reporting has led to earlier dialysis initiation.7 A second hypothesis is that there may have been changes over time in indications for dialysis not captured in available data sources,8–10 although stable levels of health care intensity around the time of dialysis initiation among Medicare beneficiaries do not seem to support this possibility.11 A third hypothesis is that trends in eGFR at initiation may reflect a progressive liberalization of guideline criteria for dialysis initiation from the late 1990s onward to promote initiation at higher levels of eGFR, especially among patients with relatively soft uremic signs and

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symptoms.1,12 Because prior studies have relied on data sources that did not include detailed information on clinical presentation at the time of initiation, little evidence is available to either support or refute the role of changing clinical indications for dialysis over time.1–5,13 To address this knowledge gap, we designed a study using detailed information from the system-wide electronic medical record of the Department of Veterans Affairs (VA) to examine temporal trends in eGFR in relation to the clinical context of dialysis initiation.

RESULTS
Cohort members who initiated dialysis in fiscal years (FYS) 2005–2009 were, on average, older and more likely to be white compared with those who initiated dialysis in FYS 2000–2004 (Table 1). Patients who initiated dialysis during the more recent time period had a higher prevalence of diabetes, a higher median risk score, and a similar prevalence of other comorbid conditions compared with those who initiated dialysis in the earlier time period. Median eGFR slope and number of visits to a VA nephrologist during the year before initiation were also similar across time periods. Patients initiating hemodialysis during the more recent time period were more likely to do so with an arteriovenous fistula.

There were no significant changes over time in the percentage of patients who were acutely ill—that is, hospitalized for sudden decline in clinical status—at the time of dialysis initiation (49.8% versus 49.7%; P=0.99) or the percentage for whom the decision to appeared to be based only on their level of estimated kidney function (4.5% versus 5.8%; P=0.23). Most patients who were not acutely ill at the time of initiation had one or more signs and/or symptoms consistent with advanced kidney disease that were either stable or gradually worsening. There were no statistically significant differences over time in the types of clinical signs and/or symptoms documented around the time of initiation, with gastrointestinal and cardio-pulmonary signs and/or symptoms being the most frequently documented during both time periods (Figure 1). Most patients had documented signs and/or symptoms in at least two different categories (median=2; interquartile range=1–3 in both time periods).

From 2000–2004 to 2005–2009, mean eGFR at dialysis initiation increased from 9.8±5.8 to 11.0±5.5 ml/min per 1.73 m² (P<0.001), the percentage of patients with an eGFR=10–15 ml/min per 1.73 m² increased from 23.4% to 29.9% (P=0.002), and the percentage with an eGFR>15 ml/min per 1.73 m² increased from 12.1% to 16.3% (P=0.01). After stratification by illness acuity and types of signs and/or symptoms, there was a statistically significant increase in mean eGFR at initiation over time for all subgroups.

After adjustment for illness acuity, documented clinical signs and/or symptoms, and patient characteristics at the time of initiation, the odds of initiating dialysis at an eGFR=10–15

Table 1. Patient characteristics by time period of initiation

<table>
<thead>
<tr>
<th>Year of Initiation</th>
<th>2000–2004 (n=826)</th>
<th>2005–2009 (n=865)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (SD), yr</td>
<td>62.0 (11.4)</td>
<td>63.5 (11.1)</td>
<td>0.003</td>
</tr>
<tr>
<td>Nonwhite race, %</td>
<td>47.3</td>
<td>40.4</td>
<td>0.004</td>
</tr>
<tr>
<td>Women, %</td>
<td>1.3</td>
<td>2.0</td>
<td>0.31</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>56.5</td>
<td>66.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ischemic heart disease, %</td>
<td>29.9</td>
<td>31.6</td>
<td>0.46</td>
</tr>
<tr>
<td>Congestive heart failure, %</td>
<td>29.5</td>
<td>32.8</td>
<td>0.14</td>
</tr>
<tr>
<td>Peripheral arterial disease, %</td>
<td>6.4</td>
<td>5.8</td>
<td>0.59</td>
</tr>
<tr>
<td>Stroke, %</td>
<td>4.5</td>
<td>5.3</td>
<td>0.43</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease, %</td>
<td>15.0</td>
<td>16.3</td>
<td>0.47</td>
</tr>
<tr>
<td>Median risk score (25th, 75th percentiles)</td>
<td>2.0 (1.3, 2.9)</td>
<td>2.3 (1.5, 3.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Died within 1 yr of initiation, %</td>
<td>17.1</td>
<td>15.4</td>
<td>0.35</td>
</tr>
<tr>
<td>Mean eGFR at initiation (SD), ml/min per 1.73 m²</td>
<td>9.8 (5.8)</td>
<td>11.0 (5.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median interval between most recent eGFR and initiation (25th, 75th percentiles), d</td>
<td>2 (1, 6)</td>
<td>1 (1, 7)</td>
<td>0.71</td>
</tr>
<tr>
<td>Median eGFR slope (25th, 75th percentiles), ml/min per 1.73 m² per yr</td>
<td>−13.7 (−7.4, −21.6)</td>
<td>−14.1 (−7.8, 24.2)</td>
<td>0.07</td>
</tr>
<tr>
<td>Inpatient initiation, %</td>
<td>74.9</td>
<td>74.6</td>
<td>0.86</td>
</tr>
<tr>
<td>Access used at initiation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peritoneal dialysis catheter, %</td>
<td>5.3</td>
<td>4.3</td>
<td>0.002</td>
</tr>
<tr>
<td>Hemodialysis fistula, %</td>
<td>16.3</td>
<td>21.9</td>
<td></td>
</tr>
<tr>
<td>Hemodialysis graft, %</td>
<td>4.6</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Hemodialysis catheter, %</td>
<td>73.7</td>
<td>71.6</td>
<td></td>
</tr>
<tr>
<td>Median outpatient VA nephrology visits (interquartile range)</td>
<td>3 (0–6)</td>
<td>3 (1–6)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

*During the year before initiation.
Between FYs 2000 and 2009, there was an upward trend in eGFR at initiation among a national cohort of patients for whom the decision to initiate dialysis was made within the VA system. This trend was not explained by changes in clinical presentation over time: neither the percentage of patients presenting with an acute illness nor the distribution of different types of clinical signs and/or symptoms at the time of dialysis initiation changed appreciably during this time period.

Our findings seem to indicate that dialysis initiation practices have changed over time to embrace higher threshold levels of eGFR as being appropriate for dialysis initiation across a wide range of different clinical contexts. As for other populations, temporal trends in eGFR at initiation among members of this cohort did not seem to be driven by changes in case mix at the time of initiation. Although patients who initiated dialysis during the later time period were older and had a higher burden of comorbidities than those who initiated dialysis during the earlier time period, the association of time period with level of eGFR at initiation persisted after adjustment for differences in patient characteristics. Detailed medical record review also provided no support for the hypothesis that an upward trend in eGFR at initiation reflected changes in clinical presentation at the time of dialysis initiation. Neither acuity level nor the types of clinical signs and/or symptoms documented around the time of initiation changed appreciably over time, and the association between time period and eGFR at initiation was still present after adjustment for these aspects of the clinical presentation. Trends in eGFR at initiation also did not reflect a greater tendency to initiate dialysis in asymptomatic patients based only on their estimated level of kidney function. Although treatment decisions were occasionally driven by level of kidney function in the absence of other clinical signs and symptoms, this practice was no more common in recent compared with earlier years.

Although an upward trend in eGFR over time was present, regardless of illness acuity or types of documented signs and symptoms, there were notable differences in the magnitude of change in eGFR over time depending on clinical context. An increase in the percentage of patients initiating dialysis at very high levels of eGFR (>15 ml/min per 1.73 m²) was present only among those who were not acutely ill at the time of initiation or had documented fatigue and/or weakness and gastrointestinal signs and/or symptoms. Among patients who were acutely ill or had cardiopulmonary signs and/or symptoms, there was an increase in the percentage with an eGFR=10–15 ml/min per 1.73 m² but not in the percentage with higher levels of eGFR. We suspect that a selective increase in the frequency of dialysis initiation at very high levels of eGFR among patients with softer indications for dialysis probably reflects the effect of changes in opinion-based clinical practice guidelines for dialysis initiation from the late 1990s onward. In 1997, the National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative (KDOQI) guideline for peritoneal dialysis adequacy recommended that dialysis be initiated at a GFR of approximately 10.5 ml/min per 1.73 m², except in the “complete absence of clinical signs and symptoms attributable to uremia.” The 2001 update of this guideline recommended dialysis initiation at GFR levels as high as 20 ml/min per 1.73 m².
in patients with protein energy malnutrition.\textsuperscript{15,16} By 2006, KDOQI was suggesting that “particular clinical considerations and certain characteristic complications of kidney failure may prompt initiation of therapy before stage 5.”\textsuperscript{17–19} In addition to traditional indications, such as intractable volume overload, hyperkalemia, and pericarditis, this list also included relatively nonspecific signs and symptoms, such as “unexplained decline in functioning or well-being” and “weight loss or other evidence of malnutrition.”\textsuperscript{17–19} This more liberal approach to dialysis initiation at higher levels of eGFR was facilitated by active collaboration between KDOQI and the Health Care Financing Administration to eliminate restrictions on the upper limit of renal function at which dialysis could be initiated without triggering a renal network review.\textsuperscript{16}

Most members of this real-world cohort of patients initiating maintenance dialysis had documented signs and/or symptoms consistent with advanced kidney disease at the time of initiation. These are precisely the patients for whom the relative benefits and harms of the observed trend toward earlier initiation of dialysis at higher levels of eGFR are not known. Many uremic signs and symptoms are common and relatively nonspecific (e.g., fatigue, nausea, malaise, and weakness), often leading to uncertainty in the clinical setting about etiology and the likely effect of dialysis. Observational data showing that symptom burden and quality of life are similar among patients with advanced kidney disease who are and are not treated with dialysis have highlighted a critical knowledge gap about the effect of dialysis on symptom burden.\textsuperscript{20–22} Although alternative treatments (e.g., diuretics, low-protein diet, anion binding resins, and antiemetics) and approaches to care (e.g., palliative care) do exist, available trial data do not address the effectiveness of these alternatives compared (or combined) with dialysis in symptomatic patients, including the effect on symptom burden.\textsuperscript{6–23} The Initiating Dialysis Early and Late (IDEAL) trial showed that delaying initiation until lower levels of eGFR in patients followed closely by a nephrologist did not result in
higher mortality, worse quality of life, or other adverse clinical outcomes. However, more than one in three patients randomized to the late start arm of the IDEAL trial initiated dialysis before reaching their target eGFR. Uremic symptoms were cited as a reason for initiation in more than one half of these patients. A smaller trial of dialysis versus a very low-protein diet in adults older than 70 resulted in similar mortality and lower hospitalization rates for patients in the diet compared with dialysis arm. Patients randomized to the diet arm started dialysis a median of 9 months after enrollment, mostly because of volume overload or hyperkalemia. However, the trial excluded patients with uremic signs and symptoms at baseline. More evidence on the benefits and harms of dialysis versus alternative approaches to the care of symptomatic patients with advanced kidney disease is needed to support discussions with patients and their families about whether and when to initiate dialysis.

Our study has the following limitations. First, the study was restricted to patients for whom the decision to initiate dialysis was made within the VA. Thus, it is possible that our results may not be generalizable to other practice settings and populations. Second, a total of 859 patients included in the chart review sample initiated dialysis outside the VA. Because level of acuteness may influence whether decisions about dialysis initiation are made within the VA (e.g., urgent presentation to a non-VA hospital), our study may underestimate the percentage of patients within the VA who are acutely ill at the time of initiation. Third, although inclusion of information on clinical presentation at the time of initiation represents an important strength of this study, these analyses do not account for clinical signs and/or symptoms that were not documented in the electronic medical record. However, we found that decisions about dialysis initiation were generally quite well documented, and it is reassuring that one or more signs and/or symptoms were documented in the electronic record for the majority of patients included in the analytic sample. Fourth, the relatively small sample size limited the precision of estimates of trends in eGFR at initiation in stratified analyses.

An upward trend in eGFR at dialysis initiation within the VA health care system from 2000 to 2009 seems to reflect changes in the timing of dialysis initiation among patients with similar indications rather than changing indications over time.

CONCISE METHODS

Cohort
Our goal was to identify a cohort of patients within the VA who initiated dialysis over a 10-year period from FY 2000 to FY 2009 and for whom the decision to initiate dialysis was made within the VA. First, we designed a procedure code search of VA inpatient and outpatient administrative and fee basis files (that record care outside the VA that is paid for by the VA) to identify a denominator population that was receiving maintenance dialysis within or paid for by the VA during this time frame. Operationally, we defined maintenance dialysis as having a procedure code for hemodialysis recorded on 15 separate days over a 60-day window or a single procedure code for peritoneal dialysis within the ascertainment period. This step yielded a cohort of 18,739 potentially eligible patients.

Second, we conducted a detailed medical record review among a random sample of these patients to identify a subset who met study inclusion criteria. For feasibility purposes, medical record review was restricted to a random sample of 3000 patients stratified by year of dialysis initiation. After reviewing the electronic medical records of these patients, we excluded 49 patients because they had not received maintenance dialysis during the observation period, 190 patients because the actual date of first dialysis documented in the electronic medical record occurred outside the observation period, 859 patients because the decision to initiate dialysis occurred outside the VA, 132 patients because a serum creatinine measurement within 45 days before dialysis initiation was not available in national VA sources, and 79 patients because the electronic medical record did not include adequate documentation of clinical presentation at the time of dialysis initiation. The remaining 1691 patients comprised the analytic cohort for this study. Compared with those excluded, patients in the analytic cohort were older (mean age=62.7±1.3 versus 60.9±11.6 years; P<0.001) but had similar median risk scores and a similar gender and racial composition.

Data Sources
Patient demographic and clinical characteristics were ascertained from a variety of different sources, including the VA enrollment file, Vital Status file, inpatient and outpatient treatment files, Decision Support System (DSS), and system-wide electronic medical record (VistAWeb) combined with Medicare inpatient and outpatient claims. Comorbid conditions were ascertained using diagnostic and procedure codes from both VA and Medicare inpatient and outpatient administrative data over the 1-year period before initiation. Information on serum creatinine measures before dialysis initiation and during the preceding 1-year period was ascertained from the VA DSS Laboratory Results (LAR) file. Date of death was ascertained from the VA Vital Status file. We used VistAWeb to access clinician notes (including those from physicians, nurses, and social workers) around the time of initiation to ascertain the true date of first dialysis, whether patients were acutely ill at the time of initiation, signs and/or symptoms documented around the time of initiation, dialysis modality and access used at the first dialysis session, and whether the patient initiated dialysis in the hospital. We used outpatient VA administrative data and Medicare claims to ascertain the number of outpatient nephrology visits within the VA during the year before initiation.

Chart Abstraction
First, B.W. (a physician assistant and trained chart abstractor) reviewed the electronic medical record of all 3000 patients to identify a subset potentially eligible for study inclusion and ascertain the date of first dialysis, dialysis modality, and type of access at the time of initiation. This step yielded a total of 1735 patients potentially eligible for inclusion. Second, A.M.O. (a practicing nephrologist with more than a decade of clinical experience caring for patients with kidney disease) reviewed the electronic medical records of these patients to
confirm cohort eligibility and ascertain each patient’s clinical presentation at the time of initiation. An additional 44 patients who did not meet cohort entry criteria were excluded in this step, yielding an analytic cohort of 1691 patients.

We used an inductive approach to characterize clinical presentation at the time of initiation on the basis of common themes identified in the electronic medical record of cohort patients. We developed classifications to characterize both overall clinical presentation and the types of clinical signs and/or symptoms documented in the electronic medical record around the time of initiation. Overall clinical presentation was characterized as whether the patient appeared to be acutely ill at the time of initiation. Patients were considered to be acutely ill if they started dialysis during a hospital admission for sudden worsening in their clinical status, regardless of whether the acute illness was directly related to their kidney disease or whether the acute symptoms had resolved at the time of dialysis initiation (Supplemental Table 1). Patients who were electively admitted to the hospital for the sole purpose of initiating dialysis were not classified as acutely ill unless they became acutely ill before dialysis initiation. For some patients, the decision to initiate dialysis seemed to be based primarily on their level of estimated kidney function, and signs and/or symptoms of advanced kidney disease were not documented or noted to be absent.

Documented signs and/or symptoms were grouped as follows: gastrointestinal, cardiopulmonary, fatigue and/or weakness, electrolyte abnormalities, neurologic (including difficulty sleeping), and other (including bleeding, hiccups, pruritis, and mention of uremia or uremic symptoms without additional specification). Patients could have symptoms falling within more than one of these groups. Supplemental Table 1 illustrates how notes from the electronic medical record were used to construct variables describing patients’ clinical presentation at the time of dialysis initiation.

To assess the precision of ascertainment of illness acuity and clinical signs and symptoms from the electronic medical record by A.M.O., S.P.W. and M.K.Y. (senior fellows in nephrology) independently reviewed the electronic medical records of a random sample of 50 cohort members. Percentage of agreement with A.M.O. ranged from 76% to 92% across items (Supplemental Table 2). The $k$-statistic ranged from 0.51 (signifying moderate agreement among the three expert reviewers) to 0.82 (signifying near perfect agreement) across items.27

To understand each patient’s clinical presentation, we started by reviewing notes from nephrologists and nephrology fellows entered around the time of initiation. We then reviewed progress notes from nephrologists and nephrology fellows entered during the 1-year period before initiation, whether dialysis was initiated in the hospital, the number of VA outpatient nephrology visits during the 1-year period before initiation, and access used at first dialysis (peritoneal dialysis catheter, arteriovenous fistula, arteriovenous graft, or hemodialysis catheter). We used a mixed model to estimate eGFR slope for each patient using all inpatient and outpatient serum creatinine measurements from the DSS LAR file during the 1-year period before initiation.

**Analyses**

We used chi-squared, $t$, and Mann–Whitney $U$ tests as appropriate to compare the characteristics of patients who initiated dialysis in FYs 2000–2004 with those of patients who initiated dialysis in FYs 2005–2009. We used logistic regression analysis to examine the association between time period of dialysis initiation (FYs 2005–2009 versus FYs 2000–2004) and level of eGFR at initiation (categorized as $<10$ [reference], 10–15, and $>15$ ml/min per 1.73 m$^2$). Multivariate analyses were adjusted for baseline patient characteristics at the time of initiation, documented clinical signs and/or symptoms, and whether the patient was acutely ill at the time of initiation. Multivariate analyses were repeated after stratification by level of acuity and types of documented signs and/or symptoms at the time of dialysis initiation. This research was approved by the Institutional Review Board at the VA Puget Sound Healthcare System.

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DISCLOSURES
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