Early Nephrology Referral 6 Months Before Dialysis Initiation Can Reduce Early Death But Does Not Improve Long-Term Cardiovascular Outcome on Dialysis

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Background: There is a paucity of studies on whether early referral (ER) to nephrologist could reduce cardiovascular mortality on dialysis, and the length of pre-dialysis nephrological care needed to reduce mortality on dialysis.

Methods and Results: A total of 604 consecutive patients who started dialysis between 2001 and 2009 in Senshu region, Osaka, Japan were analyzed. Non-linear associations between mortality and pre-dialysis duration of nephrological care were assessed using restricted cubic spline function, and predictors for death analyzed on Cox modeling. A total of 31.6%, 18.2%, 11.3% and 6.1% of patients had >12, 24, 36 and 48 months of pre-dialysis care, respectively. A total of 258 patients (42.7%) were categorized as ER (≥6 months pre-dialysis duration). During the follow-up period (median, 31.1 months), 218 patients died (cardiovascular, n=70; infection, n=69). Although patients with late referral (LR) had a proxy of inappropriate pre-dialysis care compared with the ER group, Cox multivariate analysis failed to show a favorable association between ER and cardiovascular outcome. In contrast, a deleterious effect of LR on overall survival was observed but was limited only to the first 12 months of dialysis (HR, 1.957; 95% CI: 1.104–3.469; P=0.021), but not observed thereafter.

Conclusions: Current pre-dialysis nephrological care may reduce short-term mortality but may not improve cardiovascular mortality after dialysis initiation. (Circ J 2016; 80: 1008–1016)

Key Words: Cardiovascular mortality; Chronic kidney disease; Dialysis; Nephrology referral

Cardiovascular disease is a leading cause of mortality in end-stage kidney disease (ESKD) patients on dialysis.1–3 Moreover, the prevalence of cardiovascular disease increases in proportion to the decline in renal function in patients with chronic kidney disease (CKD).4 Despite the considerable resources committed to the care of ESKD patients and improvement in quality of dialysis treatment, the mortality among dialysis patients remains high.1–3 Therefore, specific risk factor reduction strategies are needed to reduce cardiovascular burden in patients with CKD. Early referral (ER) to nephrologists and regular specific care of patients with CKD during the pre-dialysis period might be expected to improve cardiovascular and nutritional conditions at dialysis initiation, leading to greater survival in patients on dialysis. Previous studies have identified a favorable association between ER to nephrologists before dialysis initiation and survival on chronic dialysis.5–9 In these studies, ER was arbitrarily defined as 3–6 months of nephrological care before dialysis initiation. It is not plausible, however, for nephrologists to be able to control the complex conditions associated with CKD (eg, hypertension, anemia, mineral bone disorders, metabolic disorders, etc) in only several months before dialysis initiation. Furthermore, these studies showed a favorable association between ER and overall survival rather than cardiovascular outcome. To our knowledge, there is a paucity of studies on the effect of referral timing to nephrologists on cardiovascular mortality, and
the length of time needed to improve survival in patients on dialysis. Thus, the aim of the present study was to explore whether ER to nephrologists could improve cardiovascular mortality and to identify the appropriate pre-dialysis duration of nephrological care needed to reduce all-cause and cardiovascular mortality in patients on chronic dialysis.

Methods

Patients

The present study was performed according to the guidelines of the Declaration of Helsinki. The study was conducted in accordance with the institutional ethics guidelines of each hemodialysis site (IRB/Ethics committee approval No. 286). Informed consent for follow-up survey was obtained from each participant at dialysis initiation. The present subjects consisted of 682 consecutive patients who started dialysis between 2001 and 2009 at Rinku General Medical Center and at another 5 hospitals located in Senshu region, Osaka, Japan. The present hospital (Rinku General Medical Center) is a tertiary-care institution and deals with approximately 70% of patients newly starting dialysis in this region. These 5 hospitals are community based and have dialysis centers (Nagayama Hospital, Nogami Hospital, Habara Hospital, Tamai Internal Medicine and Orthopedic Hospital and Nishide Hospital) dealing with the remaining 30% of dialysis initiation. Patients who started dialysis at Rinku General Medical Center (n=487), except for those receiving peritoneal dialysis (PD) care at the PD clinic, transferred to one of 34 community-based hemodialysis sites including the aforementioned 5 hospitals and were prospectively followed, whereas patients who started dialysis at the other 5 hospitals (n=195), were surveyed retrospectively. Twenty-three patients were excluded from the analysis due to pre-emptive renal transplantation (n=6), discontinuation of hemodialysis (n=2), terminal malignancy (n=8) or loss to follow-up (immediately after transfer to a hemodialysis site, n=7). The remaining 55 patients were also excluded because of a lack of sufficient baseline data at the start of dialysis and because of loss to follow-up due to transfer to other hospitals. After exclusion, 604 patients were available for the current analysis.

Data Collection and Definition

Data for 464 of the patients were retrieved from the prospective inception cohort at Rinku General Medical Center. At the end of each year, follow-up information regarding 94% of patients was gathered from medical records and local physicians. Information regarding the remaining 6% of patients was obtained using a physician questionnaire. The data for 140 patients from the other 5 hospitals were collected from their medical records and from local physicians. Demographics (age, gender), cause of ESKD, comorbid conditions (history of cardiovascular and cerebrovascular disease), smoking, predialysis erythropoiesis-stimulating agents (ESA) use and clinical and laboratory variables (blood pressure, heart rate, serum creatinine, hemoglobin, albumin, total cholesterol, calcium, phosphate, intact parathyroid hormone, ferritin, C-reactive protein [CRP] and HbA1c) were obtained immediately before initiation of dialysis. Glomerular filtration rate at dialysis initiation was estimated using the formula for Japanese subjects (estimated glomerular filtration rate (eGFR) \( \text{[ml/min/1.73 m}^2\] = \(194 \times \text{serum creatinine}^{1.094} \times \text{Age}^{-0.287} \times 0.739 \) [if female]).

Echocardiogram was performed according to the recommendations of the American Society of Echocardiography at dialysis initiation. Left ventricular (LV) mass was calculated using the formula of Devereux and Reichek and indexed to body surface area as LV mass index (g/m²). Brain natriuretic peptide (BNP) was measured using chemiluminescent microparticle immunoassay (Abbott Laboratories) and cardiac troponin T (cTnT) was measured using second-generation electrochemiluminescence immunoassay (Roche Diagnostic). Furthermore, information on emergency induction of dialysis, uremic symptoms (defined as consciousness disorder, digestive organ symptoms such as severe nausea with sometimes vomiting or persistent diarrhea and extreme physical weakness), volume overload (defined as orthopnea, dysnea or low oxygen saturation <95% accompanied by congestion, pulmonary edema or massive pleural effusion on chest X-ray) and type of vascular access at dialysis initiation was also retrieved from medical records.

Timing of referral to nephrologists was evaluated using categorical variables in which the pre-dialysis duration with nephrological care was dichotomized arbitrarily: ER, referred to nephrologists at ≥6 months before the first chronic dialysis; late referral (LR), referred <6 months before the first chronic dialysis. The definition of ER varied among the previous studies (3–6 months), 6,8 and 6 months before dialysis initiation was the most frequently used, although there was no evidence to back up this definition. Deaths were reviewed and assigned an underlying cause by local physicians and one of the study authors (T.H.). Cardiovascular death was defined as death due to heart failure, myocardial infarction, arrhythmia, infectious endocarditis, aortic aneurysm, sudden death or other cardiovascular diseases, and cerebrovascular death was defined as death due to stroke or other cerebrovascular diseases. Causes of infectious death were categorized into sepsis, pneumonia, infection of central nervous system, digestive system or urinary tract, hepatitis and tuberculosis according to the classification of death in the annual survey of the Japanese Society of Dialysis Treatment. Furthermore, death was dichotomized according to length of time from dialysis initiation: early death, death <12 months after dialysis initiation; late death, death at ≥12 months after dialysis initiation. The endpoint of this study was all-cause and cardiovascular death. These endpoints were analyzed at the end of December 2009. The median follow-up period was 31.1 months (range, 1–107.2 months).

Statistical Analysis

Continuous variables are presented as median (IQR). Continuous variables were compared using the Mann-Whitney U-test. Categorical variables were compared using chi-squared test. Patient follow-up started at the first dialysis treatment. Death from any cause was assessed. Rates of death were compared using Kaplan-Meier survival curves and log-rank test with a 2-sided a level of 0.05. Multicollinearity was assessed and an interaction was observed between referral timing and predialysis ESA use. To assess the non-linear relationship between pre-dialysis period of nephrological care and mortality risk, we used a restricted cubic spline model. Furthermore, we evaluated the proportional assumption using Schoenfeld residuals, and all covariates except for gender satisfied this. We then used the stratified Cox proportional hazard model by gender to estimate the risk of referral timing to nephrologists for all-cause and cardiovascular mortality, using hazard ratio (HR) and 95% CI. Given that the relatively small number of events per variable meant that multivariate analysis for the predictors of cardiovascular and early death was less conservative, subgroup analysis was performed to evaluate confounding as much as possible. All data were analyzed using
of cardiovascular disease including heart failure, coronary artery disease or peripheral artery disease, cerebrovascular disease and DN was similar in the 2 groups, the proportion of patients with emergency dialysis induction (P=0.000), uremic symptoms (P=0.001), volume overload (P=0.000) and temporary catheter use (P=0.000) was higher in the LR group compared with the ER group. Furthermore, mean blood pressure (MBP), heart rate, ferritin and CRP were significantly higher (P=0.003, P=0.000, P=0.001, P=0.000, respectively) and prevalence of pre-dialysis ESA use was lower (P=0.000) in the LR group compared with the ER group. Of note, patients with LR started dialysis at higher eGFR than those with ER (P=0.007).

A total of 404 and 246 patients had echocardiogram data and cardiac biomarker data such as BNP and cTnT, respectively. Ejection fraction (EF) was significantly lower and deceleration time shorter, whereas BNP and cTnT were significantly higher in the LR group compared with the ER group (P=0.000, 0.000, respectively). SPSS version 11 and R statistics version i386.3.1.0. P<0.05 was considered significant.

Table 1. Baseline Characteristics vs. Referral Time to Nephrologist

| Total          | Early referral (n=258) | Late referral (n=346) | P-value (early vs. late) |
|----------------|------------------------|-----------------------|--------------------------|
| Age (years)    | 68 (60–76)             | 67 (58–74)            | 70 (62–78)               | 0.004                      |
| Male gender    | 342 (56.6)             | 215 (59.7)            | 188 (54.3)               | 0.213                      |
| Etiology       |                        |                       |                          |                           |
| CGN            | 139 (23.0)             | 84 (32.6)             | 55 (15.9)                | 0.000                      |
| DN             | 251 (41.6)             | 113 (43.8)            | 138 (39.9)               | 0.000                      |
| BNS            | 135 (22.4)             | 39 (15.1)             | 96 (27.7)                |                           |
| Other          | 79 (13.0)              | 22 (8.5)              | 57 (16.5)                |                           |
| Past history   |                        |                       |                          |                           |
| Cardiovascular | 144 (23.8)             | 62 (24.0)             | 82 (23.7)                | 0.923                      |
| Heart failure  | 56 (9.3)               | 23 (8.9)              | 33 (9.6)                 | 0.887                      |
| Coronary artery disease | 77 (11.6) | 28 (10.9) | 49 (14.2) | 0.267 |
| PAD            | 8 (1.3)                | 2 (0.8)               | 6 (1.7)                  | 0.477                      |
| Cerebrovascular| 97 (16.1)              | 37 (14.3)             | 60 (17.3)                | 0.370                      |
| Smoking        | 251 (41.6)             | 115 (44.6)            | 136 (39.3)               | 0.277                      |
| Duration before RRT (months) | 4 (0–17) | 21 (11–37) | 0 (0–3) | 0.000 |
| Pre-dialysis ESA use | 308 (51.0) | 221 (85.7) | 87 (25.1) | 0.000 |
| Emergency induction | 112 (18.5) | 16 (6.2) | 96 (27.7) | 0.000 |
| Uremic symptoms| 51 (8.4)               | 11 (4.3)              | 40 (11.6)                | 0.001                      |
| Volume overload| 57 (9.4)               | 12 (4.7)              | 45 (13.0)                | 0.000                      |
| Temporary catheter use | 341 (56.5) | 84 (32.6) | 257 (74.2) | 0.000 |
| SBP (mmHg)     | 152 (136–170)          | 149 (134–168)         | 158 (138–172)            | 0.004                      |
| DBP (mmHg)     | 80 (68–88)             | 78 (64–86)            | 80 (70–90)               | 0.020                      |
| Mean BP (mmHg) | 103 (91–114)           | 100 (89–111)          | 104 (93–116)             | 0.003                      |
| Heart rate (beats/min) | 76 (68–84) | 74 (66–82) | 77 (70–86) | 0.000 |
| Creatinine (mg/dl) | 8.10 (6.20–10.00) | 8.42 (6.70–10.56) | 7.80 (5.80–9.66) | 0.001 |
| eGFR (ml/min/1.73 m²) | 5.26 (4.12–6.93) | 4.94 (4.00–6.63) | 5.40 (4.30–7.22) | 0.007 |
| Hemoglobin (g/dl) | 8.7 (7.4–9.6) | 8.8 (7.6–9.8) | 8.6 (7.4–9.5) | 0.084 |
| Albumin (g/dl) | 3.1 (2.8–3.6)          | 3.1 (2.8–3.5)         | 3.2 (2.8–3.6)            | 0.564                      |
| Total cholesterol (mg/dl) | 162 (136–193) | 162 (139–191) | 162 (135–193) | 0.681 |
| Calcium (mg/dl) | 8.6 (7.9–9.2) | 8.5 (7.9–9.2) | 8.7 (8.0–9.2) | 0.256 |
| Phosphate (mg/dl) | 5.8 (4.8–6.9) | 5.8 (4.8–6.7) | 5.8 (4.8–7.2) | 0.605 |
| Intact PTH (pg/ml) | 211 (130–323) | 230 (146–362) | 192 (114–289) | 0.001 |
| Ferritin (mg/ml) | 188.4 (84.1–336.0) | 158.5 (80.5–274.4) | 207.5 (94–385.2) | 0.001 |
| CRP (mg/dl)    | 0.4 (0.1–1.8)          | 0.2 (0.1–0.9)         | 0.7 (0.2–2.83)           | 0.000                      |
| HbA1c (%)      | 5.6 (5.1–6.3) (n=342) | 5.7 (5.2–6.3) (n=146) | 5.5 (5.0–6.4) (n=106) | 0.270                      |

Data given as median (IQR) or n (%). BNS, benign nephrosclerosis; BP, blood pressure; CGN, chronic glomerulonephritis; CRP, C-reactive protein; DBP, diastolic BP; DN, diabetic nephropathy; eGFR, estimated glomerular filtration rate; ESA, erythropoiesis-stimulating agent; PAD, peripheral artery disease; PTH, parathyroid hormone; RRT, renal replacement therapy; SBP, systolic BP.

Results

Baseline Characteristics vs. Referral Timing

Baseline characteristics at dialysis initiation by referral timing (ER vs. LR) are listed in Table 1. Overall, median patient age was 68 years and 56.6% were male. The primary cause of ESKD was diabetic nephropathy (DN; 41.6%) followed by chronic glomerulonephritis (CGN; 23.0%), benign nephrosclerosis (BNS; 22.4%) and other etiologies (Other; 13.0%). Median eGFR at dialysis initiation was 5.26 ml/min/1.73 m². These data were similar to those reported by the Japanese Society of Dialysis Treatment. A total of 346 patients (57.3%) were categorized as LR. Patients with LR were significantly older than those with ER (P=0.004). Although the frequency of cardiovascular disease including heart failure, coronary artery disease or peripheral artery disease, cerebrovascular disease and DN was similar in the 2 groups, the proportion of patients with emergency dialysis induction (P=0.000), uremic symptoms (P=0.001), volume overload (P=0.000) and temporary catheter use (P=0.000) was higher in the LR group compared with the ER group. Furthermore, mean blood pressure (MBP), heart rate, ferritin and CRP were significantly higher (P=0.003, P=0.000, P=0.001, P=0.000, respectively) and prevalence of pre-dialysis ESA use was lower (P=0.000) in the LR group compared with the ER group. Of note, patients with LR started dialysis at higher eGFR than those with ER (P=0.007). A total of 404 and 246 patients had echocardiogram data and cardiac biomarker data such as BNP and cTnT, respectively. Ejection fraction (EF) was significantly lower and deceleration time shorter, whereas BNP and cTnT were significantly higher in the LR group compared with the ER group (P=0.000, 0.000, respectively).
Early Nephrology Referral and CV Mortality

Recently, pre-dialysis duration <6 months (LR) was the most frequently observed regardless of CKD etiology, and the proportion of the patients with >12, 24, 36 and 48 months of pre-dialysis nephrological care was 31.6%, 18.2%, 11.3% and 6.1%, respectively (data not shown).

Furthermore, cardioprotective agents were more frequently used in the ER group than in the LR group (Table S1).

Median pre-dialysis duration of the CGN, DN, BNS and Other groups was 11, 4, 2 and 0 months, respectively. Importantly, pre-dialysis duration <6 months (LR) was the most frequently observed regardless of CKD etiology, and the proportion of the patients with >12, 24, 36 and 48 months of pre-dialysis nephrological care was 31.6%, 18.2%, 11.3% and 6.1%, respectively (data not shown).

**Table 2. Indicators of All-Cause Mortality**

|                               | Univariate analysis | Multivariate analysis |
|-------------------------------|--------------------|----------------------|
|                               | HR     | 95% CI  | P-value | HR     | 95% CI  | P-value |
| Referral timing*               | 1.378  | 1.041–1.824 | 0.025  |        |        |        |
| Age                           | 1.068  | 1.054–1.083 | 0.000  | 1.072  | 1.054–1.091 | 0.000  |
| Etiology (vs. CGN)             |        |        |        |        |        |        |
| DN                            | 1.052  | 0.719–1.538 | 0.796  | 0.969  | 0.646–1.452 | 0.878  |
| BNS                           | 2.755  | 1.844–4.116 | 0.000  | 0.943  | 0.593–1.499 | 0.803  |
| Other                         | 2.301  | 1.455–3.638 | 0.000  | 1.946  | 1.192–3.174 | 0.008  |
| Cardiovascular history         | 0.579  | 0.431–0.780 | 0.000  |        |        |        |
| Cerebrovascular history        | 1.678  | 1.214–2.320 | 0.002  |        |        |        |
| Smoking                       | 1.404  | 1.020–1.933 | 0.038  | 1.571  | 1.097–2.250 | 0.014  |
| Pre-dialysis ESA use           | 0.624  | 0.475–0.819 | 0.001  |        |        |        |
| Emergency induction           | 1.197  | 0.869–1.649 | 0.271  |        |        |        |
| Uremic symptoms               | 0.856  | 0.540–1.356 | 0.507  |        |        |        |
| Volume overload               | 1.203  | 0.805–1.799 | 0.367  |        |        |        |
| Temporary catheter use         | 1.580  | 1.191–2.095 | 0.002  |        |        |        |
| eGFR                          | 1.125  | 1.081–1.170 | 0.000  | 1.072  | 1.016–1.130 | 0.011  |
| Albumin                       | 0.326  | 0.047–2.286 | 0.258  |        |        |        |
| Hemoglobin                    | 1.060  | 0.979–1.149 | 0.152  |        |        |        |
| Calcium                       | 1.444  | 1.253–1.664 | 0.000  | 1.293  | 1.104–1.516 | 0.001  |
| Phosphate                     | 0.846  | 0.777–0.921 | 0.000  |        |        |        |
| Ln iPTH                       | 0.686  | 0.595–0.792 | 0.000  |        |        |        |
| Ln ferritin                   | 1.176  | 1.019–1.358 | 0.027  |        |        |        |
| Total cholesterol             | 0.995  | 0.992–0.998 | 0.001  |        |        |        |
| Ln CRP                        | 3.352  | 2.415–4.651 | 0.000  | 2.100  | 1.442–3.058 | 0.000  |
| Mean BP                       | 0.991  | 0.983–0.999 | 0.024  |        |        |        |
| Heart rate                    | 1.026  | 0.948–1.110 | 0.527  |        |        |        |

Proportional assumption was violated by gender, therefore Cox models were stratified by gender. *Dichotomized as 6 months before dialysis initiation. HR, hazard ratio; iPTH, intact parathyroid hormone. Other abbreviations as in Table 1.

Figure 1. Unadjusted Kaplan-Meier curves for (A) overall survival and (B) cardiovascular death-free survival vs. referral timing.
As shown in Table 2, on univariate Cox analysis the referral timing to nephrologists was significantly associated with all-cause mortality, whereas this association was not statistically significant on multivariate analysis, although higher age, etiology of CKD, smoking habit, higher eGFR at dialysis initiation, higher calcium and higher CRP were independently associated with all-cause death. Nevertheless, there was a clear overall survival difference between the 2 groups during the first year of dialysis treatment (Figure 1), therefore the validity of this was tested on interval Cox models from the start of chronic dialysis to 12 months of dialysis treatment.

Indeed, on univariate analysis, the HR of LR on overall survival increased (HR, 2.851; 95% CI: 1.544–5.265; P=0.001) and remained significant on multivariate analysis (HR, 1.974; 95% CI: 1.120–3.478; P=0.019; Table 3). Furthermore, we performed sensitivity analyses to investigate the effect of referral timing before renal replacement therapy (RRT) initiation on the outcomes of death. Figure 2 shows the adjusted HR for referral timing for the outcomes adjusted for variables significantly associated with each outcome on univariate analysis. There was no significant association between any referral timing before RRT initiation and all-cause or cardiovascular death, whereas nephrology referral at 6–18 months before dialysis initiation was not associated with poor outcome.

**Table 3. Indicators of Early Death**

|                | HR       | 95% CI      | P-value |
|----------------|----------|-------------|---------|
| **Univariate analysis** |          |             |         |
| Referral timing* | 2.851    | 1.544–5.265 | 0.001   |
| Age            | 1.075    | 1.047–1.104 | 0.000   |
| Etiology (vs. CGN) |          |             |         |
| DN             | 0.542    | 0.271–1.085 | 0.084   |
| BNS            | 1.930    | 1.046–3.561 | 0.035   |
| Other          | 2.345    | 1.197–4.594 | 0.013   |
| Cardiovascular history | 1.898    | 1.125–3.203 | 0.016   |
| Cerebrovascular history | 1.345    | 0.711–2.545 | 0.362   |
| Smoking        | 1.196    | 0.655–2.184 | 0.559   |
| Pre-dialysis ESA use | 0.340    | 0.208–0.556 | 0.000   |
| Emergency induction | 2.245    | 1.304–3.865 | 0.004   |
| Uremic symptoms | 1.684    | 0.799–3.548 | 0.170   |
| Volume overload | 1.767    | 0.867–3.601 | 0.117   |
| Temporary catheter use | 3.247    | 1.725–6.113 | 0.000   |
| eGFR           | 1.152    | 1.089–2.191 | 0.000   |
| Albumin        | 0.725    | 0.484–1.086 | 0.119   |
| Hemoglobin     | 0.982    | 0.841–1.147 | 0.822   |
| Calcium        | 1.637    | 1.287–2.082 | 0.000   |
| Phosphate      | 0.899    | 0.788–1.025 | 0.113   |
| Ln iPTH        | 0.771    | 0.586–1.014 | 0.063   |
| Ln ferritin    | 1.379    | 1.069–1.778 | 0.013   |
| Total cholesterol | 0.991    | 0.985–0.997 | 0.005   |
| Ln CRP         | 5.965    | 3.480–10.225| 0.000   |
| Mean BP        | 0.977    | 0.962–0.993 | 0.005   |
| Heart rate     | 1.014    | 0.997–1.032 | 0.108   |
| **Multivariate analysis** |          |             |         |
| Referral timing* | 1.974    | 1.120–3.478 | 0.019   |
| Age            | 1.075    | 1.047–1.104 | 0.000   |
| Calcium        | 1.447    | 1.106–1.892 | 0.007   |
| Ln CRP         | 3.496    | 1.973–6.195 | 0.000   |

Proportional assumption was violated by gender, therefore Cox models were stratified by gender. *Dichotomized as 6 months before dialysis initiation. Abbreviations as in Tables 1, 2.
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RRT initiation was associated with reduction of early death. Concerning cardiovascular mortality, higher age, etiology of CKD, volume overload, and higher calcium were significantly and independently associated with cardiovascular death, but referral timing was not a predictor of cardiovascular mortality (Table 4). Contrary to expectations, uremic symptoms, emergency induction or temporary catheter use were not associated with all-cause or cardiovascular mortality on multivariate analysis. Finally, subgroup analyses stratified by age, etiology of CKD, previous cardiovascular disease, smoking status, MBP and eGFR at RRT initiation showed that there was no interaction across subgroups, except for that between MBP and referral timing on all-cause death (P=0.035) (Figure 3).

Effect of Referral Timing on Mortality Cause
Number and cause of early and late death stratified by referral pattern is listed in Table 5. There was no difference in mortality cause between the ER and the LR groups (P=0.613). Of interest, there was a significant difference in mortality cause between the early and late death. Infection was the major cause of the early death, whereas cardiovascular death was dominant in late deaths (P=0.014).

Discussion
Although previous studies showed a favorable impact of ER on overall survival on dialysis, little attention has been focused on the effect of referral timing on cardiovascular mortality on dialysis. Furthermore, few data are available on the optimal length of nephrologist care for CKD patients needed to improve all-cause and cardiovascular mortality. The present study clearly showed that >6 months (ER) of pre-dialysis nephrological care was not associated with reduction of cardiovascular mortality. Even though patients in the LR group had higher blood pressure, ferritin and CRP, such factors were not associated with cardiovascular mortality. The present study also showed that the effect of ER was limited to reduction only of early death associated with infection. The present results contradict the findings from the previous reports in which a beneficial association between ER and overall survival in patients on chronic dialysis was observed. Of note, on careful inspection of the Kaplan-Meier survival curves of the ER and LR groups in some previous studies, a steep fall was seen in the first several months in the LR group, as seen in the present study, and no difference thereafter. To our knowledge, only the Winkelmayer et al study has demonstrated the deleterious effect of LR on mortality during the first few month of dialysis initiation. They also suggested that this limited effect could be explained by survival bias. Patients who are susceptible to the effect of pre-dialysis management on comorbidity tend to die early after dialysis initiation, whereas those who do not seem to depend on pre-dialysis management, are more likely to survive. In the present study, the causes of death were different between early and late death. In early death, infection, which is susceptible to pre-dialysis care, was the dominant cause. In the annual survey of the Japanese Society of Dialysis Treatment, infectious disease was the leading cause of death in patients who had dialysis initiated in 2010 and who died by the end of 2010. A previous report clearly demonstrated that unplanned dialysis initiation was associated with infection-related death due to temporary catheter use and malnutrition. More frequent use of temporary catheter, higher CRP, higher blood pressure and infrequent ESA use in the present LR group may be a proxy for inappropriate pre-dialysis care. Furthermore, it is clinically plausible that 6 months of nephrological care may not be long enough to manage complicated conditions associated with CKD (eg, anemia, hypertension, volume overload, mineral bone disorder and so on), but is sufficient to decide on...
the optimal timing of RRT initiation, taking comorbidity into consideration. As shown by Tang et al, patients with delayed initiation of dialysis and uremic symptoms had worse outcome at 1 year compared with elective starters; the present study also found a similar association between emergency initiation of dialysis and early death on univariate analysis, albeit not on multivariate analysis. Thus, timely initiation of dialysis before appearance of uremic symptoms is crucial for improving short-term survival. In 2006, K/DOQI guideline recommended that nephrologists should evaluate the risk/benefit ratio of starting dialysis for eGFR <15 ml/min/1.73 m², and also suggested that initiation of dialysis at eGFR >15 ml/min/1.73 m² should be considered if patients had any symptoms associated with their comorbidities.

The definition of ER in the previous studies varied from 3 to 6 months before dialysis initiation, but these values were arbitrarily defined without evidence. In the present study, restricted cubic spline modeling was not able to identify the optimal duration of pre-dialysis nephrological care to reduce all-cause and cardiovascular mortality on dialysis. Jungers et al reported that beneficial effect of ER was especially apparent when nephrological care was provided at least 3 years before dialysis initiation. In the present study, the relatively short pre-dialysis care in the ER group could partly explain the reason why ER was not associated with a long-term survival advantage compared with LR. Furthermore, as we and others have already reported, the present screening strategy using cardiac biomarkers for asymptomatic coronary artery stenosis or subclinical heart failure, and frequent consultation with cardiologists, may reduce the severity or fatality rate of cardiovascular events, and such a strategy may offset the difference of the effect of referral timing on mortality.

Table 4. Indicators of Cardiovascular Death

| Univariate analysis | HR   | 95% CI  | P-value |
|---------------------|------|---------|---------|
| Referral timing*    | 1.466| 0.888–2.423 | 0.135 |
| Age                 | 1.049| 1.025–1.073 | 0.000 |
| Etiology (vs. CGN)  |      |         |         |
| DN                  | 1.812| 0.884–3.712 | 0.104 |
| BNS                 | 3.601| 1.615–8.030 | 0.002 |
| Other               | 3.390| 1.407–8.163 | 0.006 |
| Cardiovascular history | 0.374| 0.229–0.612 | 0.000 |
| Cerebrovascular history | 0.679| 0.309–1.491 | 0.335 |
| Smoking             | 1.530| 0.867–2.702 | 0.142 |
| Pre-dialysis ESA use | 0.685| 0.424–1.108 | 0.685 |
| Emergency induction | 1.588| 0.935–2.697 | 0.087 |
| Uremic symptoms     | 0.843| 0.380–1.873 | 0.676 |
| Volume overload      | 2.207| 1.233–3.953 | 0.008 |
| Temporary catheter use | 1.690| 1.016–2.810 | 0.043 |
| eGFR                | 1.145| 1.072–1.223 | 0.000 |
| Albumin             | 0.326| 0.047–2.268 | 0.258 |
| Hemoglobin          | 1.041| 0.901–1.203 | 0.585 |
| Calcium             | 1.643| 1.267–2.129 | 0.000 |
| Phosphate           | 0.906| 0.786–1.044 | 0.174 |
| Ln iPTH             | 0.685| 0.528–0.889 | 0.004 |
| Ln Ferritin         | 1.031| 0.794–1.337 | 0.820 |
| Total cholesterol   | 0.999| 0.994–1.004 | 0.643 |
| Ln CRP              | 2.619| 1.412–4.857 | 0.002 |
| Mean BP             | 0.981| 0.967–0.995 | 0.008 |
| Heart rate          | 1.012| 0.995–1.030 | 0.169 |

| Multivariate analysis | HR   | 95% CI  | P-value |
|-----------------------|------|---------|---------|
| Age                   | 1.063| 1.033–1.095 | 0.000 |
| Etiology (vs. CGN)    |      |         |         |
| DN                    | 1.569| 0.721–3.414 | 0.256 |
| BNS                   | 1.844| 0.748–4.541 | 0.183 |
| Other                 | 4.085| 1.619–10.309 | 0.003 |
| Volume overload       | 2.546| 1.362–4.762 | 0.003 |
| Calcium               | 1.515| 1.150–1.997 | 0.003 |

Proportional assumption was violated by gender, therefore Cox models were stratified by gender. *Dichotomized as 6 months before dialysis initiation. Abbreviations as in Tables 1,2.
Acknowledgments

We thank all the physicians and staff at the 34 community-based hemodialysis sites, especially Shuji Okazaki, MD, PhD (Nagayama Hospital), Hiromi Nogami, MD, PhD (Nogami Hospital), Keiji Mimura, MD, PhD (Nishide Hospital), Kinya Hamada (Daini-Nagisa Hospital) and Yasushi Saika (Kishiwada Fujii Clinic).

Conclusions

Six months of pre-dialysis nephrological care reduces early death on dialysis, but it has no effect on cardiovascular mortality on dialysis. Further studies are needed to identify the optimal duration of pre-dialysis care or establish a specific risk factor reduction strategy to reduce cardiovascular burden in patients with CKD.

Table 5. Referral Pattern vs. Time Interval and Cause of Death

| Time interval | Early referral (n=258) | Late referral (n=346) |
|---------------|------------------------|----------------------|
| Early death*  | 18                     | 62                   |
| Cardiovascular | 5                      | 16                   |
| Infection     | 6                      | 29                   |
| Malignancy    | 1                      | 5                    |
| Others        | 6                      | 12                   |
| Censored      | 240                    | 284                  |
| Late death    | 57                     | 81                   |
| Cardiovascular | 19                     | 30                   |
| Infection     | 14                     | 20                   |
| Malignancy    | 9                      | 9                    |
| Others        | 15                     | 22                   |
| Censored      | 183                    | 203                  |

*Within 12 months after initiation of renal replacement therapy.
Conflict of Interest
The authors declare no conflicts of interest.

References
1. US Renal Data System.USRDS 2013 annual data report: Atlas of chronic kidney disease and end-stage renal disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2013.
2. ERA-EDTA Registry. ERA-EDTA Registry annual report 2013. Amsterdam: Academic Medical Center, Department of Medical Informatics, 2015.
3. Nakai S, Iseki K, Itami N, Ogata S, Kazama J, Kimata N, et al. An overview of regular dialysis treatment in Japan (as of 31 December 2010). Ther Apher Dial 2012; 16: 483–521.
4. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events and hospitalization. N Engl J Med 2004; 351: 1296–1305.
5. Avorn J, Bohn RL, Levy E, Levin R, Owen WF Jr, Winkelmaier WC, et al. Nephrologist care and mortality in patients with chronic renal insufficiency. Arch Intern Med 2002; 162: 2002–2006.
6. Kinchen KS, Sadler J, Fink N, Brookmeyer R, Klag MJ, Levey AS, et al. The timing of specialist evaluation in chronic kidney disease and mortality. Ann Intern Med 2002; 137: 479–486.
7. Stack AG. Impact of timing of nephrology referral and pre-ESRD care on mortality risk among new ESRD patients in the United States. Am J Kidney Dis 2003; 41: 310–318.
8. Lin CL, Wu MS, Hsu PY, Huang CC. Improvement of clinical outcome by early nephrology referral in type II diabetes on hemodialysis. Ren Fail 2003; 25: 455–464.
9. Nakamura S, Nakata H, Yoshihara F, Kamide K, Horio T, Nakajima H, et al. Effect of early nephrology referral on the initiation of hemodialysis and survival in patients with chronic kidney disease and cardiovascular disease. Circ J 2007; 71: 511–516.
10. Jagers P, Massy ZA, Nguyen-Khoa T, Choukroun G, Robino C, Fakhouri F, et al. Longer duration of predialysis nephrological care is associated with improved long-term survival of dialysis patients. Nephrol Dial Transplant 2001; 16: 2357–2364.
11. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis 2009; 53: 982–992.
12. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. J Am Soc Echocardiogr 1989; 2: 358–367.
13. Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man: Anatomic validation of the method. Circulation 1977; 55: 618–618.
14. Durrleman S, Simon R. Flexible regression models with cubic splines. Stat Med 1989; 8: 551–561.
15. Schoenfeld D. Partial residuals for the proportional hazards model. Biometrika 1982; 69: 51–55.
16. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. Am J Epidemiol 2007; 165: 710–718.
17. Winkelmaier WC, Owen WF Jr, Levin R, Avorn J. A propensity analysis of late versus early nephrologist referral and mortality on dialysis. J Am Soc Nephrol 2003; 14: 486–492.
18. Lorenzo V, Martín M, Rufino M, Hernandez D, Torres A, Ayus JC. Predialysis nephrologic care and a functioning arteriovenous fistula at entry are associated with better survival in incident hemodialysis patients: An observational cohort study. Am J Kidney Dis 2004; 43: 999–1007.
19. Stehman-Breen CO, Sherrard DJ, Gillen D, Caps M. Determinant of type and timing of initial permanent hemodialysis vascular access. Kidney Int 2000; 57: 639–645.
20. Arora P, Obrador GT, Ruthazer R, Kausz AT, Meyer KB, Jeneulessen CS, et al. Prevalence, predictors, and consequences of late nephrology referral at a tertiary care center. J Am Soc Nephrol 1999; 10: 1281–1286.
21. Astor BC, Eustace JA, Powe NR, Klag MJ, Sadler JH, Fink NE, et al. Timing of nephrologist referral and arteriovenous access use: The CHOICE Study. Am J Kidney Dis 2001; 38: 494–501.
22. Yamauchi T, Sakata Y, Takada T, Nochioka K, Miura M, Tadaki S, et al; on behalf of the CHART-2 investigators. Prognostic impact of anemia in patients with chronic heart failure: With special reference to clinical background: report from the CHART-2 Study. Circ J 2015; 79: 1984–1993.
23. Patel L, Bernard LM, Elder GI. Sevelamer versus calcium-based binders for treatment of hyperphosphatemia in CKD: A meta-analysis of randomized controlled trials. Clin J Am Soc Nephrol 2015 December 14, doi:10.2215/CJN.06800615.
24. Tang SCW, Ho YY, Tang AWC, Cheng YY, Chiu FH, Lo WK, et al. Delaying initiation of dialysis till symptomatic uraemia: Is it too late? Nephrol Dial Transplant 2007; 22: 1926–1932.
25. National Kidney Foundation. KDOQI Clinical practice guidelines and clinical practice recommendations for 2006 updates: Hemodialysis adequacy, peritoneal dialysis adequacy and vascular access. Am J Kidney Dis 2006; 48 (Suppl 1): S1–S322.
26. Hayashi T, Obi Y, Kimura T, Iio K, Sumitsuji S, Takeda Y, et al. Cardiac troponin T predicts occult coronary artery stenosis in patients with chronic kidney disease at the start of renal replacement therapy. Nephrol Dial Transplant 2008; 23: 2936–2942.
27. Yasuda K, Kimura T, Sasaki K, Obi Y, Iio K, Yamato M, et al. Plasma B-type natriuretic peptide level predicts kidney prognosis in patients with predialysis chronic kidney disease. Nephrol Dial Transplant 2012; 27: 3885–3891.
28. Iishi J, Takahashi H, Kitagawa F, Kuno A, Okuyama R, Kawai H, et al. Multimarker approach to risk stratification for long-term mortality in patients on chronic hemodialysis. Circ J 2015; 79: 656–663.

Supplementary Files

Supplementary File 1

Table S1. Echocardiogram, cardiac biomarkers and cardioprotective agent use vs. referral timing

Figure S1. Unadjusted Kaplan-Meier curves for (A) overall survival and (B) cardiovascular death-free survival by etiology of CKD.

Figure S2. Restricted cubic spline model showing (—) relative risk with (- - -) 95% CI for the association of pre-dialysis duration of nephrological care with risk of (A) all-cause and (B) cardiovascular mortality.

Please find supplementary file(s):
http://dx.doi.org/10.1253/circj.CJ-15-1013