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Original Investigation

Hemodiafiltration Versus Hemodialysis and Survival in Patients With ESRD: The French Renal Epidemiology and Information Network (REIN) Registry

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Background: Recent randomized trials report that mortality is lower with high-convection-volume hemodiafiltration (HDF) than with hemodialysis (HD).

Study Design: We used data from the French national Renal Epidemiology and Information Network (REIN) registry to investigate trends in HDF use and its relationship with mortality in the total population of incident dialysis patients.

Setting & Participants: The study included those who initiated HD therapy from January 1, 2008, through December 31, 2011, and were dialyzed for more than 3 months; follow-up extended to the end of 2012.

Factor: HDF use at the patient and facility level.

Outcomes: All-cause and cardiovascular mortality, using Cox models to estimate HRs of HDF as time-dependent covariate at the patient level, with age as time scale and fully adjusted for comorbid conditions and laboratory data at baseline, catheter use, and facility type as time-dependent covariates. Analyses completed by Cox models for HRs of the facility-level exposure to HDF updated yearly.

Results: Of 28,407 HD patients, 5,526 used HDF for a median of 1.2 (IQR, 0.9-1.9) years; 2,254 of them used HDF exclusively. HRs for all-cause and cardiovascular mortality associated with HDF use were 0.84 (95% CI, 0.77-0.91) and 0.73 (95% CI, 0.61-0.88), respectively. In patients treated exclusively with HDF, these HRs were 0.77 (95% CI, 0.67-0.87) and 0.66 (95% CI, 0.50-0.86). At the facility level, increasing the percentage of patients using HDF from 0% to 100% was associated with HRs for all-cause and cardiovascular mortality of 0.87 (95% CI, 0.77-0.99) and 0.72 (95% CI, 0.54-0.96), respectively.

Limitations: Observational study.

Conclusions: Whether analyzed as a patient- or facility-level predictor, HDF treatment was associated with better survival.

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INDEX WORDS: Hemodialysis (HD); hemodiafiltration (HDF); treatment modality; registry-based study; epidemiology; dialysis; mortality; cardiovascular mortality; survival; end-stage renal disease (ESRD).

Hemodiafiltration (HDF), which combines diffusion and convection, improves removal of uremic toxins in the middle-molecule range. The first evidence of improved survival with HDF came in the late 2000s, from the observational DOPPS (Dialysis Outcomes and Practice Patterns Study)[1] and from a small randomized controlled study of hemofiltration.[2] At that time, the percentage of hemodialysis (HD) patients treated by HDF was low, ranging from 1.7% in Spain to 20% in Italy. The findings from DOPPS might have been confounded by indication. Three large randomized controlled trials[3-5] and 4 meta-analyses[6-9] followed, reporting different conclusions about the effects of HDF on survival. The most consistent finding was that HDF with a high, but not a low, convection volume was associated with better survival. However, this observation was based on secondary subgroup analyses. Together with the

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[*]*The dialysis facilities participating in the REIN Registry are listed in the annual report available at www.agence-biomedecine.fr/Le-programme-REIN.*

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possible harm to malnourished patients from excessive albumin loss with HDF (a drawback of this technique), as well as its higher cost, this uncertainty currently acts as a barrier to its more widespread adoption. Additional supportive evidence of its superiority to standard HD is clearly required.

To further investigate survival with HDF, we used the French Renal Epidemiology and Information Network (REIN) registry and examined the nationwide incident patient population. The large size of this registry-based population enables analyses of all-cause and cardiovascular mortality. Additional analyses by patient subgroups, defined by sex and various clinical conditions, including serum albumin status, sought to identify patients who might benefit most from HDF. We analyzed HDF as both a patient- and facility-level predictor to take indication bias into account. Finally, because the higher bacteriologic quality of the water used in HDF might explain, at least in part, the benefits found for HDF, we also separately compared outcomes of patients treated with standard HD and online HDF in the dialysis facilities offering both treatment modalities.

METHODS

Population

The REIN registry includes all patients with end-stage renal disease receiving long-term renal replacement therapy in France, either by extracorporeal renal replacement therapy or kidney transplantation. Details of the methods and quality control of the REIN registry have been described elsewhere.[10] Because of the high mortality rate during the first 90 days of dialysis treatment,[11] deaths within the first 3 months of HD were analyzed separately. This study included all incident adult patients who initiated HD therapy from January 1, 2008, through December 31, 2011, and were dialyzed for more than 3 months: 28,407 of a total of 31,850 patients (Fig 1). The REIN registry was approved by the relevant French committees, the Comité consultatif sur le traitement de l'information en matière de recherche (CCTIRS) and the Commission nationale de l'informatique et des libertés (CNIL 903188). For population-based registries requiring exhaustiveness, French regulations require that patients be informed by the clinic that they can choose not to participate (opt out).

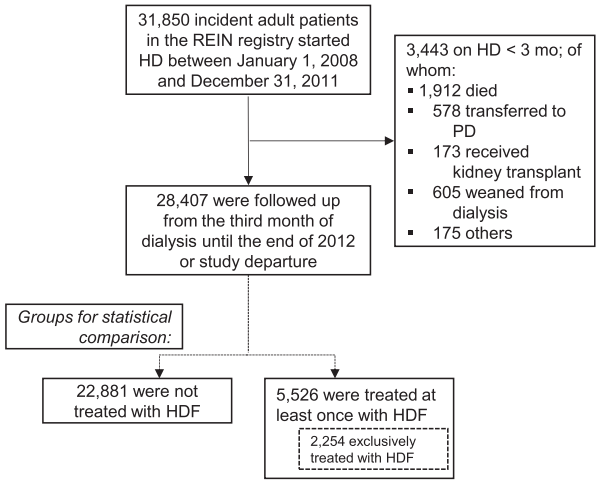

Figure 1. Flow chart of the study. Abbreviations: HD, hemodialysis; HDF, hemodiafiltration; REIN, Renal Epidemiology and Information Network.

Information

Information about patients at initiation included age, sex, primary kidney disease, comorbid conditions, disability status, body mass index, conditions of initial dialysis (including emergency status and catheter use), and laboratory data (serum albumin, creatinine, and blood hemoglobin). Estimated glomerular filtration rate (eGFR) was calculated with the 4-variable MDRD (Modification of Diet in Renal Disease) Study equation. Comorbid conditions included diabetes, heart failure, coronary heart disease, stroke, peripheral vascular disease, chronic respiratory disease, active malignancy, cirrhosis, smoking, and mobility status. Patient-level technical data included use of HDF, frequency and session length of dialysis, facility type (in-center dialysis facility, satellite facility, and self-dialysis), and dialysis facility legal status (for profit vs not for profit). Changes in facility type and legal status, dialysis modality, and vascular access are updated annually as long as the patient remains on dialysis therapy. HDF mode (pre, post, mixed, and mid) is not available from the registry.

Outcomes

Events including kidney transplantation, recovery of kidney function, and death were collected prospectively and reported from the first day of treatment. Study outcomes included overall and cardiovascular mortality. Patients were considered at risk in Cox proportional hazards models from the third month of dialysis until death or study departure due to kidney transplantation, dialysis weaning, loss to follow-up, transfer to peritoneal dialysis therapy, moving out of France, or study end (end of 2012).

Statistical Analyses

Missing data were treated by multiple imputations with a Markov chain Monte Carlo approach. We used a run length of 500 iterations and created 20 imputed data sets (SAS PROC MI; SAS Institute Inc). Variables included in the imputation procedure were age, sex, dialysis facility type and legal status, comorbid conditions and laboratory data as listed above, first dialysis with catheter, and outcome (all-cause death). Results of analyses through the 20 complete imputed data sets were combined, and the final results were averaged across these sets (SAS PROC MIANALYZE). Baseline characteristics at dialysis therapy initiation are shown as estimated mean numbers and percentages, which are compared between patients never treated by HDF and those who were treated by HDF.

Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for overall mortality were estimated by time-dependent Cox proportional hazards models stratified by region, facility type, and legal status. We used age as the time-scale to better control for the effect of age in this large-scale longitudinal study mainly composed of elderly patients.[12,13] Because of the smaller number of events, cardiovascular mortality models were stratified only by facility type and region and then adjusted for facility legal status. Because some unknown patient characteristics and medical practice patterns may vary by facility, robust variance estimates (sandwich estimators) were used to account for facility-clustering effects.[14,15] The first model was adjusted for sex. Fully adjusted models were further adjusted for baseline comorbid conditions and clinical and laboratory data, specifically diabetes, heart failure, coronary heart disease, peripheral vascular disease, stroke, myocardial infarction, chronic respiratory disease, obesity, cirrhosis, active malignancy, smoking, mobility, albuminemia, eGFR, and session length. They were also adjusted for facility