Detailed Methods

Trial Design

The Frequent Hemodialysis Network Trials have been described in detail elsewhere.[16] In the Daily Trial, 245 patients from 11 sites in the US and Canada were randomized to receive either daily hemodialysis (1.5–2.75 hours per session, 6 days per week), or conventional hemodialysis (2.5–4.5 hours per session, 3 days per week). Both groups received their hemodialysis treatments in out-patient settings. In the Daily Trial, all accesses were cannulated by nurses or dialysis technicians. In the Nocturnal Trial, 87 patients from 9 centers in the US and Canada were randomized to receive either nocturnal hemodialysis (at least 6 hours, 6 nights per week), or conventional hemodialysis. For this trial, all patients and/or their caregivers were trained to perform hemodialysis at home, including cannulation of the access. The exception was 8 conventional patients who received in-center hemodialysis according to the initial version of the protocol. Four of these patients switched to home hemodialysis during follow-up. Patients were followed for 12 months. Two co-primary and several efficacy outcomes were defined for each trial. The pre-specified major safety outcome was vascular access complications.[16]

Vascular Access Data

In addition to type and location of vascular access being used at randomization, detailed vascular access data were captured on specific event reporting forms. Research personnel recorded the start date that a new access began being used for hemodialysis to the nearest month. Whether patients were using buttonhole technique for arteriovenous access cannulation was recorded for patients in the Nocturnal Trial.

Access repair was defined as any procedure performed on the access that resulted in *continued use of the same access*. For arteriovenous fistulae and grafts, we captured angioplasty, stenting, thrombectomy, and surgical revision. For catheters, we recorded stripping of fibrin sheaths and repair of broken components. As thrombolysis of catheters using tissue plasminogen activator (tPa) was not captured accurately across all centers, we did not include thrombolysis in the final definition of repair.

Access loss was defined as *abandonment* (*i.e.,* access no longer being used), *or removal of the access for any reason.* This included replacing tunneled catheters over a wire. If a patient was using an arteriovenous fistula/graft, but then had a new tunneled catheter inserted, this was counted as an arteriovenous fistula/graft loss. Elective removals of catheters upon successful use of a new arteriovenous fistula/graft were recorded, but were not counted as events. A Vascular Access Outcomes Committee blinded to group allocation reviewed all access events to determine if the event met the definition of repair or loss.

Coordinators captured all deaths and hospitalizations on separate event forms. An independent Outcomes Committee blinded to group allocation reviewed these forms, discharge summaries, and supplementary chart information to determine whether each death or hospitalization was access- or non-access related.

Outcomes

The primary vascular access outcome was defined as the composite of time to first access repair, loss, or access-related hospitalization. If an access loss occurred within 10 days of a repair procedure, the loss was counted instead of the repair and the event date was set to the earliest repair date within the 10-day period. Pre-specified secondary outcomes were

time to any repair and time to any loss. Specific reasons for repair and loss were defined as descriptive outcomes only.

Statistical Analysis

Primary Analysis:
Data from each trial were analyzed separately. Baseline continuous variables were summarized using mean ±SD, or median with 10th and 90th percentiles for skewed data, while categorical variables were summarized using proportions. We plotted Kaplan-Meier survival curves of the risk of reaching the primary outcome for each group, and used the log-rank test to compare differences between the curves.[22] We used Cox proportional hazards models to estimate the relative change in hazard rate of the primary outcome due to daily or nocturnal hemodialysis.[23] For the Daily Trial, we adjusted for effects of clinical center. We censored patients at the time of death, transplant, or loss to follow-up in all analyses. Patients who had elective removal of a catheter when an arteriovenous fistula/graft was used were followed until the end of follow-up, or until they had an event. The proportional hazards assumption was tested and met for each analysis.

Additional Analyses:
For each trial, we repeated the primary analysis after grouping patients by access type. Those using an arteriovenous fistula or graft at randomization formed one subgroup, while those using tunneled catheters at randomization formed the other. If patients switched to the other access type before an event occurred, this was treated as a censoring event.

We evaluated the two secondary outcomes of time to all losses and time to all repairs using Andersen-Gill models, specifying a robust sandwich covariance matrix structure for intra-individual correlation.[24] Periods of arteriovenous access use were analyzed separately from periods of catheter use. If a patient was using both a catheter and an arteriovenous fistula or graft simultaneously, we considered the catheter to be the access at risk, assuming that the fistula or graft was not fully functional. For the analyses of access losses, each successive access contributed sequentially to the periods of risk with access hospitalizations and repairs being ignored. For the repairs-only analyses, losses and hospitalizations were ignored. Multiple repairs that occurred within 10 days were treated as a single repair event with the most serious repair (possibilities were ranked *a priori*) designated as the single cause and the earliest repair date within the 10 days set as the event date. Due to few catheter events, we restricted our statistical comparisons of the secondary outcomes to arteriovenous fistulae and grafts. We pre-specified combining fistulae and grafts in our main analyses of the secondary outcomes. For further information, we repeated the secondary outcome analyses in those with fistulae and grafts separately.

Finally, for patients using arteriovenous accesses in the Nocturnal Trial, we assessed the effect of using buttonhole technique on all losses, repairs or access hospitalizations. We used the Andersen-Gill model, treating buttonhole technique as a time-dependent covariate. Buttonhole status was imputed for 6.4% of patient records based on usage patterns observed among the patients' non-missing data.

Explanation for imputing buttonhole status

Indications of buttonhole status were collected monthly at varying days for each month. Changes in accesses or access events rarely occurred on the same dates as when buttonhole status was collected. The task was then to infer buttonhole status for the change-in-access or access event dates; only the designations during the event dates affected the analyses. This was done in two ways:

1) If there were no missing buttonhole indications in the monthly records just prior, during, and immediately following an access event, and if all of the indications were identical, then the buttonhole status was assumed to be the same on the date of the access event.
2) If the buttonhole indices in the period outlined above were inconsistent in any way (including cases where indications were missing) then, the monthly patterns of buttonhole status were examined on a patient-by-patient basis. Except for one case, the patterns represented continued use or disuse for multiple months, occasionally followed by a change in status, again for several months. Dates for access events almost always occurred during one of the multi-month use or non-use periods and the status during the event days were assigned accordingly.

One further note: the buttonhole indications themselves were not imputed. If no indication existed then the time-dependent covariate for buttonhole usage reflected this.