Effects of Frequent In-Center Hemodialysis: The Frequent Hemodialysis Network (FHN) Daily Trial
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Background: We conducted a randomized clinical trial to determine if frequent in-center (“daily”) hemodialysis resulted in increased left ventricular mass (LVM), self-reported physical health and other intermediate outcomes in patients on maintenance hemodialysis.

Methods: Patients were randomized to 6x versus 3x-per-week hemodialysis for 12 months. The co-primary composite outcomes were 1) death or change (baseline to 12 months) in LVM by cardiac magnetic resonance imaging (death/LVM); and 2) death or change in the RAND Physical Health Composite (PHC) from the SF-36 (death/PHC). Secondary outcomes included cognitive performance, self-reported depression, laboratory markers of nutrition, mineral metabolism and anemia, blood pressure and rates of hospitalization and vascular access interventions.

Results: Patients randomized to the 6x-per-week arm completed an average of 5.2 sessions per week; the weekly standard Kt/V was significantly higher in the 6x-per-week arm (3.54 ± 0.56 versus 2.49 ± 0.27). As expected, per-session ultrafiltration volume and interdialytic weight gain were lower, and corresponding weekly values higher, in the 6x-per-week arm. Frequent hemodialysis resulted in favorable changes in both co-primary outcomes (death/LVM hazard ratio (HR) 0.61, 95% confidence interval (95% CI) 0.46 to 0.82 and death/PHC HR 0.70, 95% CI 0.53 to 0.92). Patients randomized to 6x-per-week hemodialysis were more likely to undergo vascular access interventions (HR 1.71, 95% CI 1.08 to 2.73). Frequent hemodialysis resulted in improved control of hypertension and hyperphosphatemia; there were no significant effects on cognitive performance, self-reported depression, and of the use of angiotensin-stimulating agents.

Conclusions: Frequent hemodialysis resulted in favorable changes on death/LVM and death/PHC, but prompted more frequent vascular access interventions.

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Effects of Nocturnal Home Hemodialysis: The Frequent Hemodialysis Nocturnal Trial Michael V. Rogers,1 Alan S. Kliger,2 and the FHN Trial Group; Wake Forest University, Winston-Salem, NC; Hospital of St. Raphael, Yale University; New Haven, CT.

Background: A randomized, clinical trial was performed to determine if frequent nocturnal hemodialysis improved left ventricular (LV) mass and related quality of life.

Methods: Subjects were randomized to twice weekly hemodialysis (2.5-5 hrs/session) or nocturnal hemodialysis (6-8 hrs/session) 6 times per week. The co-primary composite outcomes were death or 12 month change in LVM by magnetic resonance imaging and 2) the RAND Physical Health Composite (PHC). Secondary outcomes included cognitive performance, self-reported depression, laboratory markers of nutrition, mineral metabolism and anemia, blood pressure and rates of hospitalization and vascular access interventions.

Results: The achieved mean (SD) weekly standard Kt/V, number of hemodialysis sessions/week and adherence to >80% of hemodialysis sessions in the conventional arm (n=42) were: 2.59 (0.69), 2.93 (0.07) and 100%, respectively; corresponding values in the nocturnal arm (n=45) were: 4.72 (1.18), 5.07 (0.79) and 75.0%, respectively. There was no significant benefit of frequent nocturnal home hemodialysis for either of the two co-primary outcomes (LV mass: Hazard ratio (HR) 0.68, 95% confidence interval (CI) of 0.44 to 1.07, p=0.097 and PHC: Hazard ratio (HR) 0.91, 95% CI 0.68 to 1.23, p=0.58). Patients randomized to the nocturnal arm experienced improved control of hyperphosphatemia and hypertension but no significant improvements in the other main secondary outcomes and a trend for an increase in vascular access events. The treatment effects on LV mass and PHC should be interpreted in the context of their wide confidence intervals. For LV mass, the large confidence interval contains the estimated effect of other randomized controlled trials showing reduced LV mass with frequent dialysis. Similarly, the change in PHC within the nocturnal arm was similar to the effect seen in the FHN Daily Trial.

Conclusions: Frequent nocturnal hemodialysis did not significantly improve the primary or main secondary outcomes except for hyperphosphatemia and hypertension.


Results from a Composite Safety Endpoint Used To Evaluate the Cardiovascular Safety of Hematide™/Peginesatide in Patients with Anemia Due to Chronic Renal Failure

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Background: Peginesatide, a PEGylated, investigational, peptide-based erythropoiesis-stimulating agent (ESA), has been studied for treatment of anemia of chronic renal failure (CRF). A Composite Safety Endpoint (CSE) was prospectively defined in the 4 Phase 3 randomized controlled peginesatide trial protocols. Pooled (across-study) analyses of the CSE were prospectively defined to evaluate cardiovascular safety of peginesatide relative to comparators (darbepoetin alfa, epoetin alfa/beta). Peginesatide met the noninferiority criterion compared to comparators in the pooled analysis. In the dialysis subpopulation, results were consistent with this finding. In the nondialysis subpopulation, an increased HR for peginesatide was observed, primarily due to a higher rate of CSE events of death, unstable angina, and arrhythmia.

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Primary Results from Two Phase 3 Randomized, Active-Controlled, Open-Label Studies (PEARL 1 and PEARL 2) of the Safety and Efficacy of Hematide™/Peginesatide for the Correction of Anemia in Patients with Chronic Renal Failure Not on Dialysis and Not Receiving Treatment with Erythropoiesis-Stimulating Agents (ESA) in patients previously treated with (CRF). EMERALD 1 and 2 were Phase 3 randomized controlled trials designed to evaluate stimulating agent (ESA), has been studied for treatment of anemia of chronic renal failure (CRF). PEARL 1 and 2 were Phase 3 randomized controlled trials that evaluated safety and efficacy of peginesatide compared to darbepoetin alfa for anemia in CRF patients not receiving dialysis or ESA treatment.

**Methods:** PEARL 1 enrolled 490 US patients; PEARL 2 enrolled 493 US and EU patients. Patients were randomized 1:1 to peginesatide once monthly starting dose 0.025 mg/kg or SC darbepoetin every 2 weeks (dose 0.75 mg/kg) titrated to maintain Hb 10-11 g/dL. Hb increase 1.0 g/dL and a Hb ≥ 11 g/dL during first 36 weeks w/o transfusions. Results were to be dosed ±52 weeks.

**Results:** In both studies, peginesatide was noninferior to darbepoetin in increasing Hb. In PEARL 2, approximately twice as many peginesatide patients received RBC transfusions; in PEARL 1, transfusion rates were similar in all treatment groups. Pooled analysis of the studies identified more deaths, unstable angina, and arrhythmia events for peginesatide than for darbepoetin.

**Primary Results from Two Phase 3 Randomized, Active-Controlled, Open-Label Studies (EMERALD 1 and EMERALD 2) of the Safety and Efficacy of Hematide™/Peginesatide for the Maintenance Treatment of Anemia in Patients with Chronic Renal Failure Who Were Receiving Hemodialysis and Were Previously Treated with Epoetin Alfa or Epoetin Beta (EMERALD 1 and 2) were Phase 3 randomized controlled trials designed to evaluate safety and efficacy of peginesatide in hemodialysis (HD) patients previously treated with epoetin alfa or beta.

**Methods:** EMERALD 1 enrolled 803 US patients; EMERALD 2 enrolled 823 US and EU patients. Patients who received HD for ≥3 months and IV or SC epoetin for 28 weeks were eligible for randomization. Patients were randomized 2:1 to receive IV or SC peginesatide once monthly or epoetin 1-time 3-weekly. Peginesatide starting dose was determined using a conversion table based on screening epoetin dose, with doses titrated to maintain target Hb 10 to 11.5 g/dL in Phase 1 and 10-12 g/dL in Phase 2. Patients were to be dosed ±52 weeks.

**Results:** In both studies, peginesatide met the primary endpoint and demonstrated noninferiority for efficacy in maintaining Hb; other efficacy endpoints were similar except for proportion in the target range in EMERALD 1. Hb excursions, excessive rates of rise, and important safety events such as death, stroke, and myocardial infarction had similar frequencies for peginesatide and epoetin.

**Conclusions:** The overall cardiovascular safety profile of peginesatide was noninferior to comparator ESA in patients with anemia of CRF. Further, in the dialysis population, the CSE was not significantly different from epoetin. Differences in the CSE in non-dialysis patients for peginesatide compared to darbepoetin warrant further evaluation.

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**Prevention of Dialysis Catheter Lumen Occlusion with rt-PS Versus Heparin (Precipit): A Randomized Trial**

**Background:** Central venous catheters (CVCs) are used for vascular access by more than 75% of incident, and up to 50% of prevalent, hemodialysis patients in North America. The optimal solution for locking CVCs to decrease the risk of catheter malfunction and bacteremia, the major complications of CVCs, is unknown.

**Methods:** We conducted a multi-centre, randomized controlled trial in 225 chronic hemodialysis patients with a newly inserted central venous hemodialysis catheter. The primary objective was to determine if substituting rt-PA (1 mg per lumen) for heparin once per week as a catheter locking solution would decrease the incidence of catheter malfunction compared to locking with heparin alone (5000 units per mL). Secondary outcomes included catheter-related bacteremia. The study treatment period was six months; participants, investigators and trial personnel were blinded to treatment allocation.

**Results:** Catheter malfunction occurred in 40 (34.8%) patients assigned to heparin and 22 (20.0%) patients assigned to rt-PA, with an almost two-fold increased risk of catheter malfunction for patients treated with heparin compared to rt-PA (hazard ratio [HR] 1.91; 95% confidence interval [CI] 1.13 to 3.22; P=0.015). Catheter-related bacteremia occurred in 16 (13.9%) patients assigned to heparin and 5 (4.6%) assigned to rt-PA (1.02 and 0.32 episodes per 1,000 patient-days in heparin and rt-PA groups; P=0.027). The risk of all-cause bacteremia was three-fold higher in the heparin compared to rt-PA arm (HR 3.16; 95% CI 1.16 to 8.61; P=0.025). The risk of adverse events, including bleeding, was similar in the two groups.

**Conclusions:** The use of once weekly rt-PA compared to heparin as a locking solution for CVCs significantly reduced the incidence of both catheter malfunction and bacteremia.

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**Should We Reduce LDL-C Cholesterol in Patients with Chronic Kidney Disease? The Results of the Study of Heart and Renal Protection (SHARP)**

**Methods:** Patients with advanced CKD (blood creatinine above 1.7 mg/dL in men or 1.5 mg/dL in women) and without known history of myocardial infarction or coronary revascularization were randomized to receive ezetimibe 10mg plus simvastatin 20mg daily versus matching placebo. The pre-specified key outcome was major atherosclerotic events (defined as first nonfatal myocardial infarction or coronary death, non-haemorrhagic stroke, coronary or non-coronary revascularization). Results: 9438 patients were randomized, of whom one third were on dialysis. Mean age was 61 years, two thirds were male, one fifth had diabetes mellitus, and one sixth had vascular disease. Among patients not on dialysis, two thirds were females. Patients with advanced CKD (blood creatinine above 1.7 mg/dL in men or 1.5 mg/dL in women) and without known history of myocardial infarction or coronary revascularization were randomized to receive ezetimibe 10mg plus simvastatin 20mg daily versus matching placebo. The pre-specified key outcome was major atherosclerotic events. Similar reductions were observed among patients who, at baseline, were or were not on dialysis. During follow-up, there were about 2100 cases of end-stage renal disease, 2000 total deaths and 900 incident cancers. Ezetimibe/simvastatin did not increase the risk of non-vascular mortality or other incidence. Conclusions: Reductions in LDL-C with ezetimibe/simvastatin safely produce substantial reductions in the risks of major atherosclerotic events among patients with CKD.

**Disclosure of Financial Relationships:** Nothing to disclose

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The Impact of Membrane Permeability and Quality of Dialysate on Cardiovascular Outcomes in Hemodialysis Patients

**Methods:** Patients were randomized, controlled, parallel-group, multi-center, placebo-controlled trial. The primary endpoint was change in Scr from baseline to 52 weeks. To determine the effect of high-flux dialyzer (HF) use on survival. The effect of high-flux dialyzer (HF) use on survival was controversial, while the effect of ultrafiltrate dialyzer (UF) use has never been investigated.

**Results:** Despite trends favoring HF and UD, primary outcome was not different between HF and LF groups and between UF and SD groups, as well as overall and CV survival and progression of CAC and IMT. In patients with arteriovenous (AV) fistula, composite CV event-free survival was higher in HF group compared to LF group (p=0.02); also overall survival and CV survival was better in HF group. In adjusted models, HF use was associated with a 39% risk reduction for composite CV events (95% CI 0.38-0.97, p=0.03). Composite CV event-free survival was higher in UF group than SD group among patients with HD duration longer than 3 years (n=399) (adjusted HR 0.55, 95% CI 0.31-0.97, p=0.04; CRP levels and CAC progression within 4 years were lower in UF group. Combined treatment with UF and HD had better overall survival rate in patients with AV fistula.

**Introduction:** The effect of high-flux dialyzer (HF) use on survival is controversial, while the effect of ultrafiltrate dialyzer (UF) use has never been investigated.

**Studies:** Patients were randomized, controlled, parallel-group, multi-center, placebo-controlled trial. The primary endpoint was change in Scr from baseline to 52 weeks. To determine the effect of high-flux dialyzer (HF) use on survival. The effect of high-flux dialyzer (HF) use on survival was controversial, while the effect of ultrafiltrate dialyzer (UF) use has never been investigated.

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**Conclusion:** Use of HF membrane improves survival in patients with AV fistula; UD provides better outcomes in patients with longer HD duration.

**Disclosure of Financial Relationships:** nothing to disclose
The Efficacy and Safety of Lixivaptan in Patients with Euvolemic Hyponatremia: Results of the LIBRA Study  

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Background: Hyponatremia is the most common laboratory abnormality in hospitalized subjects and is associated with increased mortality, cognitive impairment, gait disturbances, falls, and fractures. No prospective study has evaluated the relationship between hyponatremia symptoms and serum sodium concentrations (SNa). Lixivaptan is a vasopressin receptor antagonist that increases SNa in patients with hyponatremia without detrimental effects on vital signs, renal function, and electrolytes.

Methods: LIBRA was a multicenter, randomized, double-blind, placebo-controlled study that evaluated the impact of lixivaptan on SNa and cognitive function in patients with euvolemic hyponatremia associated with the syndrome of inappropriate antidiuretic hormone secretion. Hospitalized patients with euvolemic hyponatremia (SNa <130 mEq/L) were randomized to receive lixivaptan or placebo in addition to standard of care. Lixivaptan was titrated based on SNa from 50 mg QD to a maximum 100 mg QD or to a minimum of 25 mg QD. Patients were treated for a total of 30 days in inpatient and outpatient settings. Symptomatology was carefully evaluated at baseline to better characterize the population. The primary endpoint was change from baseline in SNa at day 7. Secondary endpoints included assessment of SNa at other time points and patients’ cognitive function using the Trail-Making Test-Part B and Medical Outcomes Study-6 cognitive function scale.

Results: From 30 July 2008 to 16 March 2010, 106 patients were enrolled in LIBRA. Results from LIBRA will be presented.

Conclusions: LIBRA will further characterize the population with euvolemic hyponatremia and establish the efficacy and safety of the vasopressin receptor lixivaptan in the treatment of this condition.

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