Intradialytic Blood Volume Monitoring in Ambulatory Hemodialysis Patients: A Randomized Trial

Donal N. Reddan,*†‡ Lynda Anne Szczech,*‡ Vic Hasselblad,* Edmund G. Lowrie,§ Robert M. Lindsay,‖ Jonathan Himmelfarb,¶ Robert D. Toto,# John Stivelman,** James F. Winchester,††‡‡ Linda A. Zillman,* Robert M. Califf,*‡ and William F. Owen, Jr‡§§

**Duke Clinical Research Institute, Duke University Medical Center, Durham, North Carolina; †University College Galway, Galway, Ireland; ‡Duke University Medical Center, Department of Medicine, Division of Nephrology, Durham, North Carolina; §Hema Metrics Inc., Kaysville, Utah; ‖London Health Sciences Center and University of Western Ontario, London, Ontario, Canada; ¶Maine Medical Center, Portland, Maine; #University of Texas Southwestern Medical Center at Dallas, Dallas, Texas; **Northwest Kidney Centers, Seattle, Washington; ††Beth Israel Medical Center, New York, New York; ‡‡RenalTech International, New York, New York; and; §§University of Tennessee, Memphis, Tennessee*

Complications related to inadequate volume management are common during hemodialysis. This trial tested the hypothesis that availability of an intradialytic blood volume monitoring (IBVM) device improves fluid removal, reducing morbidity. A six-center, randomized trial with 6 mo of intervention comparing IBVM using Crit-Line *versus* conventional clinical monitoring was conducted. The average rate of non–access-related hospitalizations was compared across treatment groups using Poisson regression. Mortality analysis used the Kaplan Meier method. A total of 227 patients were randomized to Crit-Line, and 216 were randomized to conventional monitoring. Both groups had similar baseline characteristics. During the study, no differences in weight, BP, or number of dialysis-related complications were observed. There were 120 and 81 non–access-related hospitalizations in the Crit-Line and conventional monitoring groups. The adjusted risk ratio for non–access-related and access-related hospitalization was 1.61 (95% confidence interval 1.15 to 2.25; $P = 0.01$) and 1.52 (95% confidence interval 1.02 to 2.28; $P = 0.04$) for the Crit-Line monitoring group. Mortality was 8.7% in the Crit-Line monitoring group and 3.3% in the conventional group ($P = 0.021$). Standardized mortality ratios comparing the Crit-Line and conventional monitoring groups to the prevalent hemodialysis population were 0.77 (NS) and 0.26 ($P < 0.001$). Hospitalization rates were 1.51 and 1.03 events/yr in the Crit-Line and standard monitoring groups, compared with 2.01 for the prevalent hemodialysis population. IBVM was associated with higher nonvascular and vascular access-related hospitalizations and mortality compared with conventional monitoring. The atypically low hospitalization and mortality rates for the conventional monitoring group suggest that these findings should be generalized to the US hemodialysis population with caution.

J Am Soc Nephrol 16: 2162–2169, 2005. doi: 10.1681/ASN.2004121053

Hemodialysis removes excess intravascular and extravascular volume and solutes accumulated with ESRD. Intradialytic hypotension and cramping are frequent complications of hemodialysis ascribed to excessive rate or volume of fluid removal (1). Alternatively, inadequate volume removal may lead to chronic volume overload manifest as hypertension, left ventricular hypertrophy, and congestive heart failure (2,3). Removal of excess intravascular volume is complicated by symptoms, autonomic dysfunction, preexisting cardiovascular disease, and various medications. Imprecision in volume removal compromises hemodialysis patients' outcomes, including the patient's perception of dialysis quality (4).

Medical devices that prospectively monitor blood volume have been advocated to better manage intradialytic volume removal (5). Crit-Line (Hema Metrics, Inc. [formerly In-Line Diagnostics], Kaysville, UT) was developed to assist with volume removal by providing real-time assessment of patients' intradialytic volume status. Crit-Line noninvasively monitors hematocrits by optical transmission (6). In smaller, uncontrolled studies, continuous hematocrit monitoring with Crit-Line correlated with intradialytic blood volume changes, and certain aspects of monitoring predicted intradialytic morbidity (7,8). Prompted by such findings, the Crit-Line Intradialytic Monitoring Benefit (CLIMB) Study tested the hypothesis that the availability of hematocrit-based intradialytic monitoring using Crit-Line would decrease morbidity associated with ultrafiltration in comparison with patient management using conventional clinical criteria such as symptoms, BP, weight, and physical examination.

Received December 7, 2004. Accepted April 25, 2005.

Published online ahead of print. Publication date available at www.jasn.org.

Address correspondence to: Dr. Lynda Szczech, Duke University Medical Center, Box 3646, Durham, NC 27710. Phone: 919-668-8008; Fax: 919-668-7128; E-mail: szcze001@mc.duke.edu

ISSN: 1046-6673/1607-2162

Materials and Methods

Study Rationale, Design, Monitoring, and Interventions

Because of different rates of volume removal from multiple compartments (cellular, interstitial, and vascular), inadequate fluid removal during hemodialysis may be detected by the absence of intradialytic hemoconcentration. Alternatively, excessive ultrafiltration can be detected as rapid increments in the hematocrit. By serially measuring hematocrit in the blood tubing using an external optical sensor, Crit-Line detects intravascular volume changes that occur with ultrafiltration or fluid administration during hemodialysis (6,7). Therefore, it is proposed that intravascular volume monitoring using Crit-Line may serve as a prospective management tool for fluid removal and be superior to clinical judgment (7–11).

The trial adhered to the Declaration of Helsinki. Informed consent was obtained. Patient eligibility for the CLIMB Study was defined as ESRD for ≥2 mo that required in-center hemodialysis three times a week and age 18 to 85 yr. Exclusion criteria were unmeasurable BP with a sphygmomanometer, active gastrointestinal bleeding, severe malnutrition (predialysis serum albumin <2.6 g/dl), active hematologic disease, kidney transplant or move to another dialysis unit scheduled within 12 mo of screening, malignancy requiring chemotherapy, use of Crit-Line at enrollment, and inability or unwillingness to provide informed consent. Patients were neither recruited nor excluded on the basis of previous ultrafiltration-related complications or target volumes. Patients were recruited from six dialysis programs that contributed 10 dialysis centers (Seattle, WA; Dallas, TX; Durham, NC; Washington, DC; Portland, ME; and London, Ontario, Canada).

After a 2-wk observation period, patients were randomized to 6 mo of intradialytic blood volume monitoring (IBVM) using Crit-Line or conventional clinical strategies. Practical considerations made it impossible to blind providers and patients. The site study coordinators were trained and tested on Crit-Line and then trained the clinical staffs.

Changes in intradialytic blood volume were profiled on the basis of the average slope of the change and the overall percentage change in blood volume (categories of <3%, ≥3 to <8%, and ≥8% change per hour). Changes in the profiles were intended to support modifications in the target postdialysis weight and/or antihypertensive medications. Instructions on the use of Crit-Line to monitor vascular access function were excluded to focus on volume management. Two weeks before and immediately after the intervention phase, Crit-Line was applied to all patients, and blood volume profiles were recorded and stored for subsequent analysis by Hema Metrics. The results from the first midweek dialysis session were used for assignment into one of the three aforementioned categories (9). When data from the first midweek dialysis session were not available, information from the next dialysis was substituted.

A patient monitoring and intervention algorithm was developed to assist in management for the patients who were monitored with Crit-Line (Figure 1). The primary investigators and their supporting medical staff all were experienced nephrologists with substantial experience in the care of hemodialysis patients. For all site primary investigators, Hema Metrics provided informational sessions regarding how the device had been used in previous studies. Monitors visited the sites to assess device usage and reinforce the previously provided education.

Algorithm use was encouraged but not mandated, in contrast to earlier studies (9). This design was intended to assess the therapeutic efficacy of Crit-Line in a trial that permitted voluntary nonuse of the information from the device as brought about by provider education, staffing patterns, competing dialysis unit tasks, and other non–device-related confounders. Therefore, Crit-Line was studied as a voluntary adjunct to care. No algorithms, clinical management advice, or instructions were provided to care for conventionally monitored patients. For both patient groups, no restrictions were placed on the type or the frequency of interventions to manage intradialytic complications. Achievement of conventional benchmarks for hemodialysis care were expected for all patients (12).

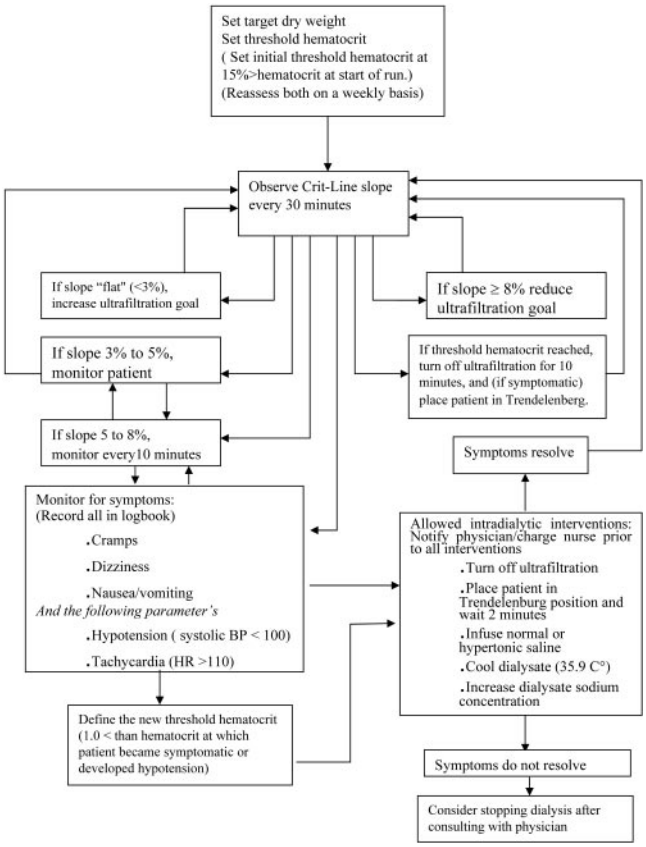

Figure 1. Recommended monitoring and intervention protocol for Crit-Line monitoring group.

The primary outcome for power calculations was hospitalization (13), based on the assumption that inadequate or overly aggressive fluid removal may independently result in increased morbidity. Hospitalizations were reported as cardiovascular, vascular access related (14,15), or other. Although hospitalizations were not centrally adjudicated, categories of hospitalization were captured and reported by the attending physicians. Several secondary measures and outcomes were selected to reflect measurements of blood volume and fluid management, including bioelectrical impedance parameters (surrogates of body water and nutritional status), pre- and postdialysis weights and BP, estimated dry weight, roentgenographic change in cardiothoracic ratio, left ventricular hypertrophy by electrocardiogram, dialysis-related complications, intradialytic interventions for volume-related signs and symptoms, angioaccess complications, and mortality.

A priori power analyses suggested that 200 patients in each arm would provide adequate power at the 93% level to demonstrate a 33% difference between treatment arms. These analyses assumed a hospitalization rate of 2.0 per year (13). Randomization was performed by permuted block within each clinical center, and randomized patients who did not complete the trial were not replaced. Compac Visual Fortran was used to generate the random allocation sequence with the seed on the basis of the second of the day. Separate sequences were created for each site. The sites provided a list of subjects to the data coordinating center. On the basis of the previously generated sequence, the treatment assignments were faxed back to the clinical sites.

The study protocol and informed consent form were reviewed and approved by local Institutional Review Boards. All patients signed an informed consent before study participation. Patient confidentiality was respected throughout.

Statistical Analyses

Baseline comparisons between groups were made using the Wilcoxon rank-sum test for continuous variables and the likelihood ratio χ^2 test for categorical variables. The average rate (incidence density) of hospitalizations was compared across treatment groups. This was defined as the total number of hospitalizations divided by the total number of person-years. As it was likely that some individuals would be much more prone to hospitalizations than others, a problem of overdispersion was anticipated. For correcting for this, the number of events for each individual was modeled using Poisson regression. The adjustments for overdispersion were made by adjusting the Hessian by the deviance (16). Length of follow-up was adjusted for by using follow-up time as an offset variable (17). The analyses were done with and without adjustment for confounding variables such as age, gender, race, primary renal diagnosis, comorbidity, etc.

Secondary measures and outcomes were analyzed using generalized linear regression models. Two-sided *P* values and 95% confidence intervals (CI) are reported. A mortality comparison between groups used the Kaplan Meier method and the log rank test.

A set of interim analyses were performed at the sponsor's request to evaluate the efficacy of Crit-Line on the basis of several secondary outcomes. Because these analyses did not involve the prespecified, primary outcome of hospitalization, adjustments for multiple comparisons were not performed.

Results

Baseline Characteristics

A total of 474 individuals were screened, and 443 were randomized between December 1999 and April 2001. A total of 227 patients were randomized to Crit-Line monitoring and 216 were randomized to conventional monitoring for 6 mo. All patients were analyzed, and their data were contributed to the analysis; patients who were lost to follow-up were censored at the point at which they were last seen (Figure 2). Overall, study patients had a mean age of 59.2 yr (median 61.0 yr), and 51% were male (Table 1). Thirty-five percent of the patients were black, 59% were white, and 6% were other races. The prevalence of diabetes and history of myocardial infarction, stroke, atrial fibrillation, or congestive heart failure were not different between the groups. Other baseline, comorbid conditions such as hypertension, peripheral vascular disease, and chronic obstructive pulmonary disease were also similar. Vascular access types were autologous fistula in 35.5%, prosthetic graft in 43.5%, and percutaneous catheter in 22%. Delivered hemodialysis doses and serum albumin, creatinine, and hemoglobin concentrations were similar in both groups at baseline.

Primary and Secondary Outcomes

During the intervention period, there were 120 non–access-related hospitalizations in the Crit-Line monitoring group and 81 non–access-related hospitalizations in the conventional monitoring group. The unadjusted risk ratio (RR) for non–access-related hospitalization was 1.49 (95% CI 1.07 to 2.08; $P = 0.017$) in the Crit-Line monitoring group as compared with the conventional group (Table 2). Although the RR for hospitalizations from cardiovascular and other causes were similar (RR = 1.47 and 1.50, respectively), of these two, only the RR for other causes achieved conventional statistical significance ($P = 0.088$ and 0.022, respectively). The rates for access-related hospitalizations were not significantly different between groups. When adjusted for dialysis site, race, gender, cause of ESRD (diabetes, hypertension, or other), age, peripheral vascular disease, chronic obstructive pulmonary disease, and cardiac disease, the RR in the Crit-Line monitoring group as compared with the conventional monitoring group for non–access-related and access-related hospitalization were 1.61 and 1.52, respectively ($P = 0.01$ and 0.04, respectively; Table 3). Further categorization of hospitalizations as cardiovascular and other yielded RR of 1.85 and 1.53, respectively ($P = 0.006$ and 0.02, respectively). The impact of dialysis center on the outcomes was tested; no significant association was noted.

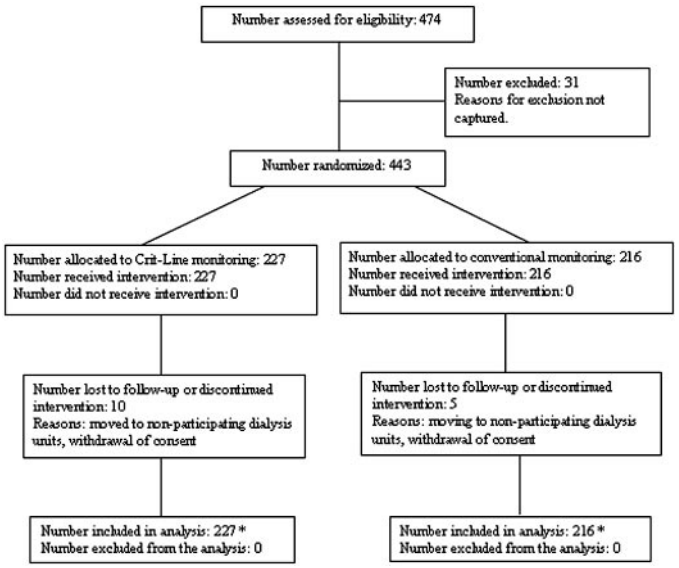

Figure 2. CONSORT patient flow diagram for the CLIMB Study.

During the intervention phase, no differences were noted between groups with respect to change in pre- and postdialysis systolic and diastolic BP ($P = 0.59$ and 0.61, respectively); estimated dry weight ($P = 0.97$); cardiothoracic ratio ($P = 0.51$); phase angle ($P = 0.67$); lean body mass ($P = 0.86$); number of antihypertensive medications prescribed ($P = 0.80$); number of hemodialysis-related complications ($P = 0.41$); number of intradialytic episodes of cramping, dizziness, or nausea ($P = 0.86$); number of hypotensive episodes ($P = 0.48$); frequency of use of intradialytic medications ($P = 0.80$); prescription of cool dialysate ($P = 0.77$) or sodium modeling ($P = 0.98$); frequency of delayed discharge from the dialysis unit ($P = 0.54$); frequency of unscheduled hemodialysis treatments (0.66); or frequency of hypoxemic episodes ($P = 0.16$; Table 4).

Mortality at 6 mo was greater in the Crit-Line than the conventional monitoring group (8.7 and 3.3%, respectively; $P = 0.021$ by log-rank test). Table 5 lists investigator-reported causes of death.

Table 1. Clinical and demographic characteristics at baseline[a]

	Crit-Line Monitoring	Conventional Monitoring	*P* Value
Age[b]	58.2 (15.9)	60.2 (15.4)	0.15
Gender (male)[c]	117 (51.5%)	109 (50.5%)	0.82
Race			
white[c]	136 (59.9%)	126 (58.3%)	0.53
black[c]	80 (35.2%)	74 (34.3%)	
other[c]	11 (4.8%)	16 (7.4%)	
Hispanic ethnicity[c]	9 (4.0%)	3 (1.4%)	0.10
Albumin (g/dl)[b]	3.7 (0.5)	3.8 (0.5)	0.92
Creatinine (mg/dl)[b]	9.4 (3.1)	9.1 (3.3)	0.17
Hemoglobin (g/dl)[b]	11.6 (1.4)	11.7 (1.4)	0.80
Angioaccess in use			
autologous fistula[c]	77 (34.1%)	75 (34.9%)	0.87
prosthetic graft[c]	101 (44.7%)	91 (42.3%)	
percutaneous catheter[c]	48 (21.2%)	49 (22.8%)	
Predialysis weight (kg)[b]	80.7 (19.9)	80.0 (23.4)	0.31
Predialysis systolic BP[b]	151.8 (26.9)	152.7 (27.1)	0.83
Predialysis diastolic BP[b]	82.0 (16.2)	80.4 (15.2)	0.51
Targeted weight (kg)[b]	77.7 (19.1)	76.5 (22.7)	0.20
Congestive heart failure[c]	41 (18.1%)	51 (23.7%)	0.15
Chronic obstructive pulmonary disease[c]	28 (12.4%)	28 (13.1%)	0.83
Diabetes[c]	98 (43.2%)	100 (46.9%)	0.43
Hypertension[c]	202 (89.0%)	189 (89.6%)	0.84
Peripheral vascular disease[c]	46 (20.4%)	40 (18.9%)	0.70
Atrial fibrillation/flutter[c]	26 (11.5%)	29 (13.4%)	0.53
Previous myocardial infarction[c]	47 (20.7%)	52 (24.1%)	0.39
Transient ischemic attacks[c]	16 (7.0%)	19 (8.9%)	0.47
Stroke[c]	32 (14.1%)	35 (16.4%)	0.50
Phase angle[b]	0.48 (0.01)	0.48 (0.01)	0.47
Left ventricular dysfunction[c]	24 (10.8%)	24 (11.3%)	0.87
Left ventricular hypertrophy[c]	52 (23.0%)	62 (29.1%)	0.15

[a]Percentages and numbers may not equal 100% as a result of rounding or missing data.
[b]Mean (SD) for continuous variables.
[c]Number (%) for categorical variables.

Table 2. Risk ratios for hospitalization (unadjusted)[a]

Hospitalization Type	Annual Event Rate		Risk Ratio		*P* Value
	Conventional	Crit-Line	Estimate	95% CI	
Non–access-related	0.77 (81)	1.15 (120)	1.49	1.07 to 2.08	0.017
cardiovascular	0.21 (22)	0.31 (32)	1.47	0.94 to 2.29	0.088
other	0.56 (59)	0.84 (88)	1.50	1.06 to 2.14	0.022
Access-related	0.26 (27)	0.36 (38)	1.42	0.93 to 2.16	0.10

[a]After the database was locked, it was discovered that the treatment group for one patient had not been recorded. This patient had been assigned to the conventional monitoring group and was included in that group for all analyses presented in this article. Another patient had been coded incorrectly as being monitored by the Crit-Line device; the patient was treated as part of the conventional monitoring group. The results contained in this table reflect the patient as receiving conventional care (as treated). Analysis performed on the database as it was locked demonstrate a relative risk (RR) of 1.51 ($P = 0.014$) for non–access-related hospitalizations and 1.71 ($P = 0.013$) for access-related hospitalizations. CI, confidence interval.

Table 3. RR for hospitalization (adjusted[a])

Hospitalization Type	RR		
	Estimate	95% CI	*P* Value
Non–access-related	1.61	1.15 to 2.25	0.01
cardiovascular	1.85	1.19 to 2.86	0.006
other	1.53	1.07 to 2.19	0.02
Access-related	1.52	1.02 to 2.28	0.04

[a]Adjusted for dialysis site, race, gender, cause of ESRD (diabetes, hypertension, other), age, peripheral vascular disease, chronic obstructive pulmonary disease, and cardiac disease.

Intradialytic Changes in Blood Volume

Highly variable implementation of the monitoring and interventional algorithm occurred within and across dialysis units; the causes were not collected. Before the intervention, 69 and 68% of patients in the Crit-Line and conventional monitoring groups, respectively, had 3 to 8% change in intravascular volume during hemodialysis (Table 6). After intervention, 68 and 65% of patients in the Crit-Line and conventional monitoring groups, respectively, had 3 to 8% change in intravascular volume. Statistical comparisons of changes in the intradialytic blood volume for individual patients was precluded by the large proportion of patients without available curves as a result of death, hospitalization, or missing data ($n = 107$; 24.1%). Because specific dialysis-related interventions were not correlated directly with the Crit-Line profiles, these interventions could not be linked to intravascular volume curves.

Comparisons with Prevalent Hemodialysis Patients

We compared the CLIMB Study patients with a contemporary US hemodialysis population to evaluate the external validity of these findings (18). The mean ages of US and CLIMB Study patients were 60.3 and 59.2 yr, respectively (NS). Fifty-one percent of CLIMB Study patients and 53.2% of US hemodialysis patients were male (NS). There were no differences in the racial distribution or the prevalence of diabetes. The annualized mortality rates in the Crit-Line and conventional monitoring groups were 17.4 and 6.4%, respectively, compared with 23.7% among US hemodialysis patients. The standardized mortality ratios for the Crit-Line and conventional monitoring groups were 0.77 (NS compared with the US hemodialysis population) and 0.26 ($P < 0.001$), respectively (19) (Table 7). The annualized hospitalization rates in the Crit-Line and conventional monitoring groups were 1.51 and 1.03 hospitalizations per year compared with 2.01 in the US hemodialysis population, respectively (13).

Discussion

In the CLIMB Study, greater non–access- and access-related hospitalizations and mortality were observed for Crit-Line than for conventional monitoring patients. Moreover, the changes of common dialysis-associated complications or need for intradialytic interventions was not different between the groups.

These findings are at odds with several previous reports (5,8–11). One potential explanation is that the greater hospitalization rate in the Crit-Line group reflects a differential vigilance or responsiveness to morbidity, suggesting that the use of IBVM should improve care: Greater hospitalizations reflect interventions to improve outcomes. However, this hypothesis is incongruous with the increased mortality among the Crit-Line monitoring group. A second potential explanation is that IBVM prompted interventions that increased morbidity and mortality for the Crit-Line monitoring group (*e.g.*, IBVM may have prompted overzealous ultrafiltration). The stable ultrafiltration profiles and volume surrogates suggest that Crit-Line did not result in an aggressive change in ultrafiltration. Although informative censoring may be present, 69 and 68% of the patients had fluid removal at the rate of 3 to 8% at the beginning and end of the CLIMB Study, respectively. Stability in this treatment parameter may reflect inaction in response to fluid removal rates outside the 3 to 8% rate or an inability to achieve fluid removal rates of 3 to 8% for a greater percentage of patients. The stability of volume surrogates across treatment groups supports that the availability of the Crit-Line did not systematically alter net ultrafiltration.

Despite the ultrafiltration profiles, the hypothesis that inaction resulted in adverse events is incongruous with the axiom that limited execution of an intervention on an experimental group biases toward the null. Instead, the findings of adverse outcome differences between the conventional and Crit-Line monitoring groups suggest that some care differences may have occurred, albeit not apparent from the rate of fluid removal and other volume-related surrogates. We are unable to define these differences. A third potential explanation is that IBVM may have distracted providers from other critical activities that affect patient outcomes. We have no data to validate this hypothesis, and no reasonable construct is available to define these behaviors.

Although the CLIMB Study patients reflected the prevalent adult ESRD population by baseline demographics and characteristics (18), their mortality and hospitalization outcomes were highly distinguishable. The patients who underwent conventional monitoring had hospitalization and death rates that were less than those in the prevalent ESRD population. Thus, in comparison with a historic control group, the Crit-Line monitoring group had no worse mortality. The conventional monitoring group had significantly better-than-expected mortality and hospitalization rates potentially related to the Hawthorne effect. Supporting this was the observation that most patients had 3 to 8% ultrafiltration at study entry. This unexpectedly high proportion (9) may reflect a higher baseline standard of care using conventional volume monitoring that continued through the intervention phase. An alternative explanation is that randomization failed to distribute equally the uncollected clinical variables that were associated with outcomes. The distribution of captured clinical parameters makes this unlikely.

From one perspective, the CLIMB Study offers statistical evidence that the availability of IBVM does not improve patients' outcomes and contributed to increased morbidity and mortality. By this data interpretation, the CLIMB Study in-

Table 4. Comparison of changes in secondary outcomes during trial between treatment groups

	Crit-Line Monitoring	Conventional Monitoring	*P* Value
Difference between pre- and postdialysis BP			
systolic	−2.11	−0.47	0.59
diastolic	−1.33	−0.16	0.61
Estimated dry weight	−0.22	−0.024	0.97
Cardiothoracic ratio	0.017	0.012	0.51
Phase angle	0.000188	−0.000015	0.67
Lean body mass	0.14	0.21	0.86
No. of antihypertensive medications			
−2	3 (1.5%)	5 (2.5%)	0.80
−1	30 (15.4%)	27 (13.7%)	
0	128 (65.6%)	129 (65.5%)	
1	28 (14.4%)	28 (14.2%)	
2	6 (3.1%)	8 (4.1%)	
missing	32	19	
Dialysis-related complications[a]	0.15	0.14	0.41
Intradialytic episodes of cramping, dizziness, or nausea[a]	0.11	0.11	0.86
Hypotensive episodes[a]	0.07	0.06	0.48
Use of intradialytic medications[a]	0.09	0.09	0.80
Prescription of cool dialysate[a]	0.02	0.02	0.77
Prescription of sodium modeling[a]	0.17	0.17	0.98
Delayed discharge from the dialysis unit[a]	0.01	0.01	0.54
Unscheduled dialysis treatments[a]	0.003	0.003	0.66
Hypoxemic episodes[a]	0.33	0.0002	0.16

[a]Expressed as total number divided by the number of patient-days at risk.

creases the list of clinical trials, casting doubt on the view that quantitative monitoring of a clinical parameter by a device is superior to clinical acumen alone. Two limitations in device performance may contribute to this disparity. The device may monitor a clinical associate, which is not a valid surrogate, or the device may offer information that is no better than clinical judgment but is associated with increased risks. Holter monitors are an example of the former (20,21), and pulmonary artery pressure catheters are an example of the latter (22–25). Thus, a cautionary note is sounded about accepting intuitively appealing medical device constructs without a formally structured evaluation of their impact on health outcomes.

Alternatively, despite the randomized trial design and consistent statistical findings, some investigators believed that clinical logic is violated by the CLIMB Study findings. First, findings of increased mortality and morbidity resulting from the extracorporeal attachment of a photometric measurement device seem clinically unreasonable. Second, nearly equivalent hospitalization risk was offered across all categories. It is difficult to understand how IBVM led to higher non–volume-related hospitalizations.

The perception that randomized, clinical trials are such a best demonstrated practice that the results are virtually irrefutable has been challenged (26,27). When clinical logic is challenged or violated substantially, structured validity analysis using analytical tools that are external to the study *per se* can be applied before broad inferences for patient care are derived (28–30). The validity analysis herein showed that the hospitalization rates and death in the conventional monitoring group were substantially lower than those in the general dialysis population. By this construct, a randomization failure, unintended selection bias, or too short observation period may account for the associations between the Crit-Line assignment and increased clinical events. However, no evidence exists for these explanations.

The CLIMB Study has a number of limitations. First, the study design does not permit us to determine the efficacy of Crit-Line had it been used more aggressively and in strict adherence to both an interpretative and a treatment pathway. The relevance of this distinction is notable; another study suggests that different results can be obtained with prescriptive IBVM in a closed feedback loop (10). Second, the study did not selectively identify and enroll patients with ongoing clinical issues of volume management. The benefit of IBVM may vary for selected patient subgroups, such as those with cardiomyopathies, dysautonomias, or large interdialytic weight gains (4). In addition, cause of hospitalization was not centrally adjudicated. Finally, the observation period used for this study was 6 mo, and the findings might have been different with a longer horizon.

In conclusion, in a randomized, controlled trial of adult hemodialysis outpatients, the availability of IBVM with Crit-Line was associated with more non–access- and access-related hos-

Table 5. Reported causes of death[a]

Patients who were randomized to Crit-Line monitoring
1. unknown; died at home, possibly cardiac related
2. sepsis, myocardial infarction
3. withdrawal of life support
4. likely diffuse multiple cerebrovascular infarcts, possibly cardiac-related
5. sepsis
6. cardiac arrest
7. cardiac arrest
8. aspiration, cardiac arrest
9. multiple myeloma
10. renal failure
11. cerebrovascular accident including intracranial hemorrhage
12. pulmonary infection (bacterial)
13. pulmonary edema
14. gastrointestinal bleed
15. assumed arrhythmia
16. suspected middle cerebral artery cerebrovascular accident
17. cerebrovascular accident
18. HIV cardiomyopathy
19. necrotizing pneumonia extensive bilateral
Patients who were randomized to conventional monitoring
1. myocardial infarction
2. withdrawal of dialysis
3. ventricular fibrillation
4. cerebrovascular accident
5. cardiac arrest, ischemic bowel
6. discontinuation of dialysis secondary to cardiomyopathy of unknown cause
7. heart failure, chronic renal failure, hypertension, hypoxia, and chronic obstructive pulmonary disease

[a]Cause(s) of death was collected as a text field in the case report form and was not adjudicated.

Table 6. Rates of fluid removal for patients before and after intervention period by treatment group[a]

	Crit-Line Monitoring Group	Conventional Monitoring Group
Preintervention profiles (per hour)		
<3%	54 (24%)	66 (32%)
≥3 and <8%	155 (69%)	125 (60%)
≥8%	17 (8%)	16 (8%)
total patients	226	207
Postintervention profiles		
<3%	41 (23%)	37 (23%)
≥3 and <8%	121 (68%)	103 (65%)
≥8%	16 (9%)	18 (11%)
total patients	178	158

[a]Data from 10 patients were missing preintervention and from 107 postintervention. Percentages were calculated by excluding patients for whom data were missing.

Table 7. Comparison of mortality by treatment groups with US Renal Data System data

	Crit-Line Group	Usual Care Group
Patients	227	216
Deaths		
observed	19	7
expected	24.7	26.8
Deaths/100 patient-years at risk		
observed	17.4	6.4
expected	22.6	24.6
Standardized mortality ratio	0.77	0.26
χ^2	1.3	14.6
P value	NS	<0.001

pitalizations and mortality than patients who received conventional monitoring. No differences in other measures that are thought to reflect intradialytic volume management were observed. Although the atypically low hospitalization and mortality rates in the conventional monitoring group may limit the external validity of the findings, the possibility exists that behaviors associated with the availability of Crit-Line in hemodialysis patients were associated with risks.

Acknowledgments

R.D.T.'s work was supported in part by grant 1K24DK02818-01A1.

These findings were presented in abstract form at the American Society of Nephrology Annual Scientific Meeting, November 2003, San Diego, CA.

The CLIMB Study was funded by Inline Diagnostics/Hema Metrics (Salt Lake City, UT). Preparation of multiple drafts and review of the final manuscript included two individuals who are affiliated with the study's sponsor and who have voluntarily withdrawn their names: Dr. David Bell, Chief Scientific Officer and member of the Board of Directors of Hema Metrics and Nancy LePaine, a former corporate officer of Hema Metrics.

References

1. Kapoian T, Sherman R. Intradialytic complications. In: *Dialysis and Transplantation: A Companion to Brenner & Rector's the Kidney*, edited by Owen W, Pereira B, Sayegh M, Philadelphia, W.B. Saunders Company, 2000, pp 199–220
2. Rahman M, Dixit A, Donley V, Gupta S, Hanslik T, Lacson E, Ogundipe A, Weigel K, Smith MC: Factors associated with inadequate blood pressure control in hypertensive hemodialysis patients. *Am J Kidney Dis* 33: 498–506, 1999
3. Parfrey PS, Harnett JD, Griffiths SM, Gault MH, Barre PE: Congestive heart failure in dialysis patients. *Arch Intern Med* 148: 1519–1525, 1988
4. Hemodialysis Adequacy Work Group. NKF/DOQI Clinical Practice Guidelines for Hemodialysis Adequacy: Update 2000. *Am J Kidney Dis.* 37: S9–64, 2001

5. Steuer RR, Germain MJ, Leypoldt JK, Cheung AK: Enhanced fluid removal guided by blood volume monitoring during chronic hemodialysis. *Artif Organs* 22: 627–632, 1998
6. Steuer RR, Harris DH, Weiss RL, Biddulph MC, Conis JM. Evaluation of a noninvasive hematocrit monitor: A new technology. *Am Clin Lab* 10: 20–22, 1991
7. Steuer RR, Leypoldt JK, Cheung AK, Harris DH, Conis JM: Hematocrit as an indicator of blood volume and a predictor of intradialytic morbid events. *ASAIO J* 40: M691–M696, 1994
8. Steuer RR, Leypoldt JK, Cheung AK, Senekjian HO, Conis JM: Reducing symptoms during hemodialysis by continuously monitoring the hematocrit. *Am J Kidney Dis* 27: 525–532, 1996
9. Howard AD, Palmer B, Howard RS, Goldberger SG, Shabshab SF: Assessing the value of blood volume monitoring to improve outcomes. A comparative observational study. *Nephrol News Issues* 12[Suppl]: 24–26, 1998
10. Santoro A, Mancini E, Basile C, Amoroso L, Di Giulio S, Usberti M, Colasanti G, Verzetti G, Rocco A, Imbasciati E, Panzetta G, Bolzani R, Grandi F, Polacchini M: Blood volume controlled hemodialysis in hypotension-prone patients: A randomized, multicenter controlled trial. *Kidney Int* 62: 1034–1045, 2002
11. Goldstein SL, Smith CM, Currier H: Noninvasive interventions to decrease hospitalization and associated costs for pediatric patients receiving hemodialysis. *J Am Soc Nephrol* 14: 2127–2131, 2003
12. Centers for Medicare & Medicaid Services: *2002 Annual Report, End Stage Renal Disease Clinical Performance Measures Project*, Baltimore, Department of Health and Human Services, Centers for Medicare & Medicaid Services, Center for Beneficiary Choices, 2002
13. US Renal Data System: *USRDS 1999 Annual Data Report*, Bethesda, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2001
14. Reddan D, Klassen P, Frankenfield DL, Szczech L, Schwab S, Coladonato J, Rocco M, Lowrie EG, Owen WF Jr; National ESRD CPM Work Group: National profile of practice patterns for hemodialysis vascular access in the United States. *J Am Soc Nephrol* 13: 2117–2124, 2002
15. NKF-K/DOQI: Clinical practice guidelines for vascular access: Update 2000. *Am J Kidney Dis* 37[Suppl 1]:S137–S181, 2001
16. SAS Institute Inc.: SAS/Stat User's Guide Version 8, Cary, SAS Institute Inc., 1999, pp. 410–411
17. SAS/Stat Software: Changes and Enhancements through Release 6.12, Cary, SAS Institute Inc., 1997, pp 272
18. US Renal Data System: *USRDS 2001 Annual Data Report*, Bethesda, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2001
19. Wolfe RA, Gaylin DS, Port FK, Held PJ, Wood DL: Using USRDS generated mortality tables to compare local ESRD mortality rates to national rates. *Kidney Int* 42: 991–996, 1992
20. The cardiac arrhythmia suppression trial. *N Engl J Med* 321: 1754–1756, 1989
21. DeMets DL, Califf RM: Lessons learned from recent cardiovascular clinical trials: Part I. *Circulation* 106: 746–751, 2002
22. Sandham JD, Hull RD, Brant RF, Knox L, Pineo GF, Doig CJ, Laporta DP, Viner S, Passerini L, Devitt H, Kirby A, Jacka M; Canadian Critical Care Clinical Trials Group: A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. *N Engl J Med* 348: 5–14, 2003
23. Connors AF Jr, Speroff T, Dawson NV, Thomas C, Harrell FE Jr, Wagner D, Desbiens N, Goldman L, Wu AW, Califf RM, Fulkerson WJ Jr, Vidaillet H, Broste S, Bellamy P, Lynn J, Knaus WA: The effectiveness of right heart catheterization in the initial care of critically ill patients. SUPPORT Investigators. *JAMA* 276: 889–897, 1996
24. Dalen JE: The pulmonary artery catheter-friend, foe, or accomplice? *JAMA* 286: 348–350, 2001
25. Polanczyk CA, Rohde LE, Goldman L, Cook EF, Thomas EJ, Marcantonio ER, Mangione CM, Lee TH: Right heart catheterization and cardiac complications in patients undergoing noncardiac surgery: An observational study. *JAMA* 286: 309–314, 2001
26. Kapatchuck TJ: The double-blind, randomized, placebo-controlled trial: Gold standard or golden calf. *J Clin Epidemiol* 54: 541–549, 2001
27. Miettinen OS, Yankelevitz DF, Henschke CI: Evaluation of screening for cancer: Annotated catechism of the Gold Standard creed. *J Eval Clin Pract* 9: 145–150, 2003
28. Chalmers TC: A potpourri of RCT topics. *Control Clin Trials* 3: 285–298, 1982
29. Yuasa H, Kurita K, Westesson PL: External validity of a randomized clinical trial of temporomandibular disorders: Analysis of the patients who refused to participate in research. *Br J Maxillofac Surg* 41: 129–131, 2003
30. Rathore SS, Weinfurt KP, Gross CP, Krumholz HM: Validity of a simple ST-elevation acute myocardial infarction risk index: Are randomized trial prognostic estimates generalizable to elderly patients? *Circulation* 107: 811, 2003