Prospective Study of Routine Heparin Avoidance Hemodialysis in a Tertiary Acute Care Inpatient Practice

Sami Safadi[1], Robert C. Albright Jr.[1], John J. Dillon[1], Amy W. Williams[1], Fares Alahdab[2], Julie K. Brown[3], Amanda L. Severson[4], Walter K. Kremers[5], Mary Ann Ryan[4] and Marie C. Hogan[2]

[1]Division of Nephrology and Hypertension, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota, USA; [2]Division of Preventive, Occupational, and Aerospace Medicine, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota, USA; [3]Nursing Practice Resources Division, Department of Nursing, Mayo Clinic, Rochester, Minnesota, USA; [4]Medical Nephrology Division, Department of Nursing, Mayo Clinic, Rochester, Minnesota, USA; and [5]Division and Biomedical Statistics and Informatics, Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota, USA

Introduction: Extracorporeal circuit (EC) anticoagulation with heparin is a key advance in hemodialysis (HD), but anticoagulation is problematic in inpatients at risk of bleeding. We prospectively evaluated a heparin-avoidance HD protocol, clotting of the EC circuit (CEC), impact on dialysis efficiency, and associated risk factors in our acute care inpatients who required HD (January 17, 2014 to May 31, 2015).

Methods: HD sessions without routine EC heparin were performed using airless dialysis tubing. Patients received systemic anticoagulation therapy and/or antiplatelets for non-HD indications. We observed patients for indications of CEC (interrupted HD session, circuit loss, or inability to return blood). The primary outcome was CEC. Logistic regression with generalized estimating equations assessed associations between CEC and other variables.

Results: HD sessions (n = 1200) were performed in 338 patients (204 with end-stage renal disease; 134 with acute kidney injury); a median session was 211 minutes (interquartile range [IQR]: 183–240 minutes); delivered dialysis dose measured by Kt/V was 1.4 (IQR: 1.2 Kt/V 1.7). Heparin in the EC was prescribed in only 4.5% of sessions; EC clotting rate was 5.2%. Determinants for CEC were temporary catheters (odds ratio [OR]: 2.8; $P < 0.01$), transfusions (OR: 2.4; $P = 0.04$), therapeutic systemic anticoagulation (OR: 0.2; $P < 0.01$), and antiplatelets (OR: 0.4; $P < 0.01$). CEC was associated with a lower delivered Kt/V (difference: 0.39; $P < 0.01$). Most CEC events during transfusions (71%) occurred with administration of blood products through the HD circuit.

Discussion: We successfully adopted heparin avoidance using airless HD tubing as our standard inpatient protocol. This protocol is feasible and safe in acute care inpatient HD. CEC rates were low and were associated with temporary HD catheters and transfusions. Antiplatelet agents and systemic anticoagulation were protective.

ClinicalTrials.gov Identifier: NCT02086682.

The introduction of unfractionated heparin to prevent clotting of the extracorporeal (EC) circuit was one of the key advances that led to the rapid development and expansion of hemodialysis (HD),[1] and it remains a mainstay in HD practice. However, anticoagulation during HD for patients at high risk of bleeding remains a frequently encountered problem. The need for anticoagulation to prevent clotting of the EC (CEC) and the need to prevent anticoagulation-related bleeding complications have led to the development of numerous strategies, the safest being, from a bleeding standpoint, anticoagulant-free HD.[2,3]

One strategy to achieve anticoagulant-free HD is to administer saline flushes through the dialysis circuit. This technique was first described in 1979,[4] and various saline-flushing protocols have since been

Correspondence: Marie C. Hogan, MD, PhD, Division of Nephrology and Hypertension, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA. E-mail: Hogan.Marie@mayo.edu

published.[5–7] The process generally involves infusing saline boluses of 100 to 200 ml every 15 to 60 minutes, which results in clotting events that require a change of dialyzer in 3% to 10% of sessions.[8,9] Other strategies include the use of heparin-coated dialysis membranes, regional heparin anticoagulation with protamine reversal, and regional citrate anticoagulation.[1,10,11] None of these techniques have been widely adopted because they are complex, and require additional time and personnel resources for administration and monitoring.

Factors that contribute to CEC include exposure to a foreign surface, exposure to air, and turbulent blood flow in the circuit.[1] Advancements in dialysis technology allow airless tubing systems that minimize blood−air interaction. One example is the Streamline (SL) bloodlines[12] (NxStage Medical, Inc., Lawrence, Massachusetts), which is designed to eliminate blood−air contact in 2 ways: a pressure pod measures arterial and venous pressures without blood−air contact; and a venous chamber runs without an air gap. The tubing allows blood to flow in a circular, nonturbulent manner, with less blood exposure to plastic than the conventional ReadySet (NxStage Medical, Inc., Lawrence, MA) bloodlines. Several small studies have shown that SL bloodlines improve dialysis efficiency and blood flow rates while reducing heparin usage.[13–15] None of these studies examined the rates of CEC or studied the problem in acutely ill inpatients at increased risk of both bleeding and thrombosis, because all these studies were performed in outpatient dialysis settings.[16,17]

Although quality information exists for outpatient HD procedures, robust data are lacking regarding inpatient dialysis anticoagulation and CEC practices and outcomes. Thus, the goal of this study was to prospectively examine CEC rates in our inpatient HD practice. We examined risk factors for CEC, the effect of CEC on HD efficiency, and the effects of systemic anticoagulation and antiplatelets on CEC (ClinicalTrials.gov Identifier NCT02086682).

MATERIALS AND METHODS

Study Population
We conducted a prospective cohort study of consecutive adult patients (age older than 18 years) who presented for inpatient dialysis at our facilities from January 17, 2014 to May 31, 2015 (Figure 1). The study was conducted in 2 stages, first in general care patients
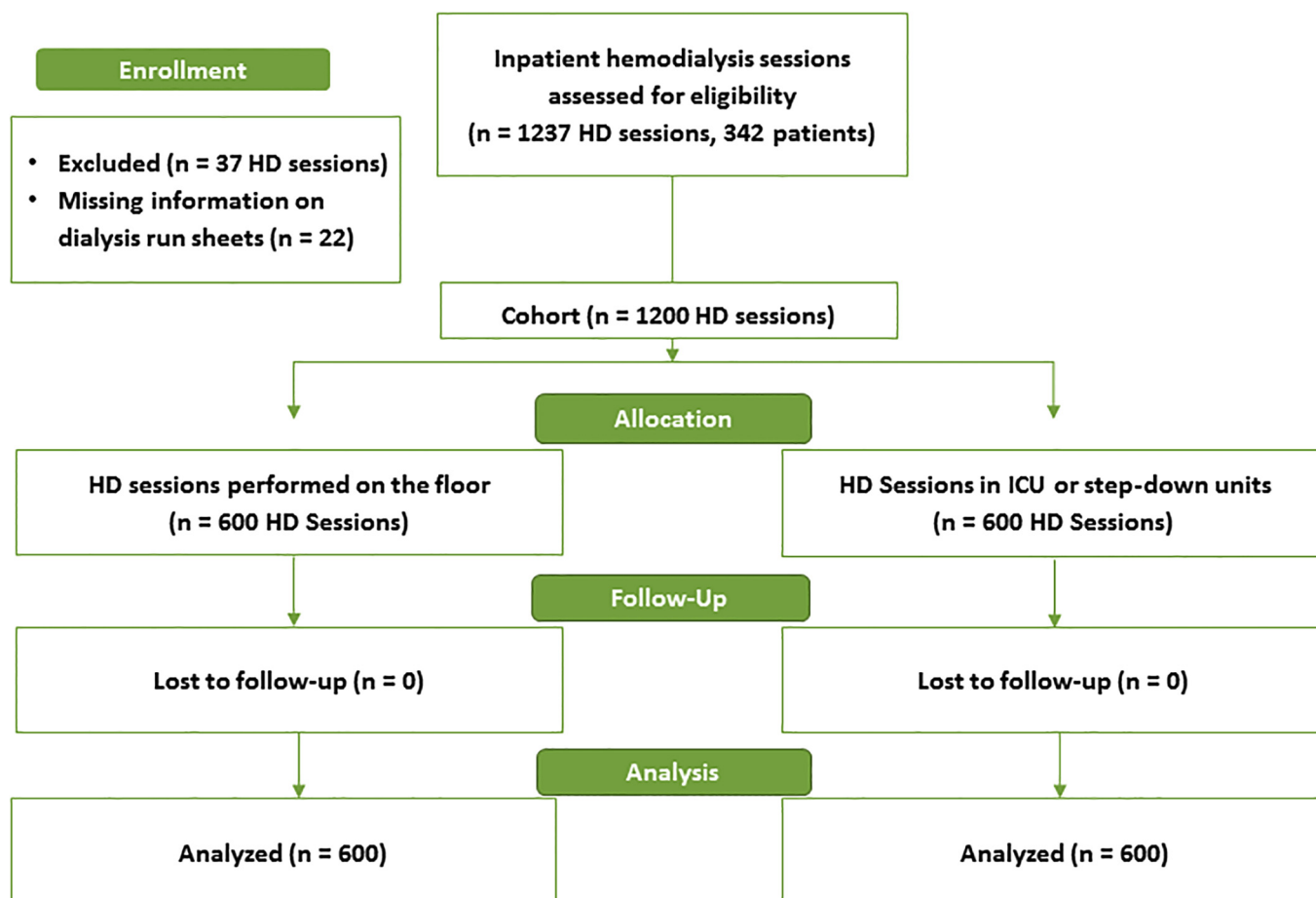

Figure 1. Study design and enrollment of subjects. No patients were lost to follow-up. HD, hemodialysis.

and then in critically ill patients. The study was approved by the Mayo Clinic Institutional Review Board in accordance with the Declaration of Helsinki and the Health Insurance Portability and Accountability Act. All patients consented to use of their medical records for research, and informed consent was waived by the institutional review board. The study was performed in Mayo Clinic Hospital, Saint Marys Campus, a 1265-bed, level 1 trauma center that provides acute medical and surgical care, including cardiac surgery, and in the Methodist Campus, a 794-bed surgical hospital that provides obstetric, hematology, oncology, liver, and kidney transplantation services in Rochester, Minnesota. Hospital services also include a 24 hours a day, 7 days a week inpatient dialysis practice staffed by 16 staff nephrologists, 2 nurse practitioners, 30 dialysis nurses, and 5 technicians performing >8000 inpatient HD sessions and continuous renal replacement therapy annually. The data were collected in 2 stages, and the cohort was divided into 2 groups: (i) 600 serial HD sessions were prospectively observed in inpatients on general care floors; and (ii) 600 serial HD sessions were observed in patients hospitalized in intensive care and step-down progressive care units.

Equipment and Implementation

The HD equipment in our hospital units is standardized to the Fresenius 2008K system (Fresenius Medical Care, Inc., Waltham, MA) with standardized prescriptions, electronic dialysis order sets, medical record documentation, and dedicated core HD nursing dialysis support personnel. SL long tubing sets (manufacturer number SL200M2095L) designed for the Fresenius 2008 series machines were implemented across all inpatient units in 2011 (Figure 2). In this study design, with consistent dialysis machine pump calibration and tubing, but variation in the complexity of the inpatient population who required dialysis, it was considered inappropriate to design a control arm with standard tubing that required anticoagulation. Standard dialysis procedures use Polyflux Revaclear 300 single-use dialyzers (Baxter, Illinois), with a 1.4-m^2 surface area, priming volume of 84 ml, polyarylethersulfone, and polyvinylpyrrolidone membrane. For individuals with allergies to this membrane or previous dialyzer reactions, the Exeltra 190 membrane (Baxter; product code 5M2121; Cellulose Triacetate: 1.9 m^2; priming volume, 84 ml, gamma sterilized) is used. For patients with known EC heparin use (typically patients with end-stage renal disease [ESRD] and individuals who had frequent dialyzer clotting), heparin was ordered, using 1 of 4 heparin regimens: (i) heparin 2000 IU prime followed by 1000 IU/h; (ii) 2000 IU prime and no maintenance; (iii) heparin 1000 IU prime and 500 IU/h;

and (iv) heparin custom priming dose, followed by custom dose maintenance per hour of dialysis. Thromboelastograhy and endogenous thrombin potentials were not performed. Post-testing of key aspects needed to be completed before the in-service training. Using SL tubing minimizes the air–blood interface because the traditional venous drip chamber is replaced with pods that measure arterial and venous pressures. The visual clotting scale ("post-rinse back guide" provided by the sponsor; see its protocol in the Supplementary Document 1 and Supplementary Table S1) was taught to all staff before study initiation. A nephrology clinical nurse specialist validated reliability of the visual clotting scale. All staff demonstrated competency and consistent practice in dialysis equipment use, tubing setup and priming, and visual clotting scale assessment. The quality of circuit degassing was assessed as optimal, with special attention to remove air from the line and dialyzer cartridge. All clinical HD technician staff watched a 28-minute clinical training video provided by the manufacturer and took a post-test written assessment that examined key aspects of the new tubing and machine set up (see Supplementary Document 2). Hands-on training (2 hours) of all clinical HD technicians of dialysis tubing and machine setup was completed using the newly calibrated dialysis machines, and participants were subsequently examined with a test of competency.

Data collection and quality was monitored by study staff (MAR, SS, MCH) and shared at weekly updates and staff meetings. Conversion to SL tubing was rolled out in a staged fashion (initially trialing 4 HD machines in July 2011), and technicians calibrated and converted all pump circuits, venous drip bulbs, and pumps to the new tubing on the day preceding the full clinical implementation date. The team subsequently committed to transition to SL tubing on all adult machines and provided dialysis staff with education, training, and a description of the research goals of this study. To guard against inadvertent use, only SL tubing was available in the hospital stock.

Exposure Assessment

Each dialysis session was prospectively observed for CEC. Events were defined as the interruption of HD session, loss of the HD circuit, or inability to return blood to the patient upon rinse back. In addition, CEC was assessed based on the visual clotting scale, and scores were subsequently calculated based on that scale. All dialysis nursing staff were trained to perform this measurement before study implementation. We tested reproducibility of the scoring and confirmed good interobserver reproducibility (Pearson $r = 0.8$). Information pertinent to dialysis sessions was
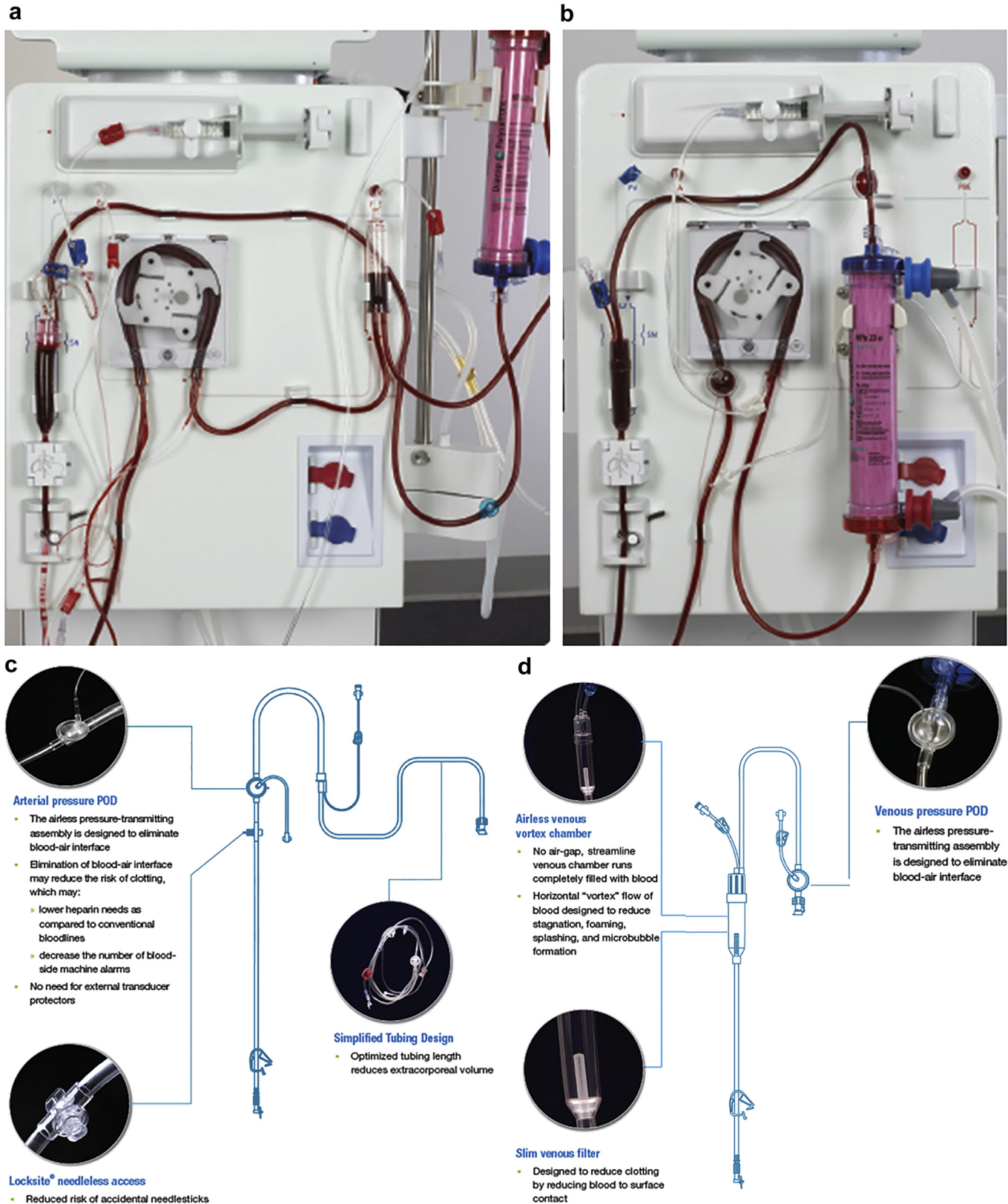
a

b

c

Arterial pressure POD

- The airless pressure-transmitting assembly is designed to eliminate blood-air interface
- Elimination of blood-air interface may reduce the risk of clotting, which may:
  - » lower heparin needs as compared to conventional bloodlines
  - » decrease the number of blood-side machine alarms
- No need for external transducer protectors

Simplified Tubing Design

- Optimized tubing length reduces extracorporeal volume

Locksite® needleless access

- Reduced risk of accidental needlesticks

d

Airless venous vortex chamber

- No air-gap, streamline venous chamber runs completely filled with blood
- Horizontal "vortex" flow of blood designed to reduce stagnation, foaming, splashing, and microbubble formation

Venous pressure POD

- The airless pressure-transmitting assembly is designed to eliminate blood-air interface

Slim venous filter

- Designed to reduce clotting by reducing blood to surface contact

Figure 2. Comparison of (a) conventional hemodialysis (Readyset) bloodlines and (b) airless (Streamline) bloodlines. (c) Arterial side of the Streamline blood lines and (d) the venous side of the Streamline bloodlines. (Adapted from Medisystems: A NxStage Company. Streamline [brochure]. Lawrence, MA: NxStage; 2014. Used with permission. Figure © 2014 NxStage Medical, Inc. Medisystems, ReadySet, and Streamline are registered trademarks of NxStage Medical, Inc. Dialog+ is a registered trademark of B. Braun Medical Inc. Fresenius and 2008 are trademarks of Fresenius Medical Care Holdings, Inc. or its affiliated companies. Caution: Federal law restricts this device to sale by or on the order of a physician. APM552 Rev. B.)

prospectively gathered through HD session sheets and custom case report forms at each session that detailed CEC and graded these events. Clinical information (demographics, hospital diagnoses, laboratory values, and medication administration) was obtained from electronic health records. Diagnosis codes were extracted from the electronic health record to calculate Charlson comorbidity scores.[17]

Outcomes

The primary outcome was the rate of CEC in the 2 prespecified groups. We examined the effect of CEC on dialysis dose. The dialyzer clearance of urea measured by (Kt/V) was derived using an online clearance monitoring algorithm based on conductivity variation installed on the dialysis machine.[18–20] We also examined the correlation between the visual scale and the significance of the CEC. We attempted to identify risk factors for CEC. We explored the effect of systemic anticoagulation and antiplatelet treatment on CEC and short-term mortality (30 day).

Statistical Analyses

Descriptive statistics were reported as counts and percentages for categorical variables, means $\pm$ SDs for unimodal, well-behaved variables, and medians and interquartile ranges for multimodal, skewed, or heavy-tailed variables. Baseline characteristics for patients and dialysis sessions were compared by t-test, Mann-Whitney U, or χ^2 proportion tests, as appropriate.

To explore determinants of CEC, logistic regression with a generalized estimating equation was performed with CEC as the dependent variable. The generalized estimating equation confirmed the appropriate analysis of patients who had >1 dialysis session. The same technique was used to test the association between systemic anticoagulation and antiplatelet medication and CEC. To explore robustness of the findings, we repeated the analysis based upon the subset of patients who did not receive EC heparin during dialysis. Statistical analyses were performed using R 3.1.3 with "gee-pack" and "survival" packages (www.r-project.org, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline Characteristics

Between January 2014 and May 2015, 1200 HD sessions were prospectively followed in 338 patients (Figure 1). The cohort was subdivided into general care (medical and surgical) patients and critical care patients based on the location of the HD session (Table 1). Thirty-eight patients who received dialysis at both sites were categorized based on where they received dialysis more frequently, and, if at both sites, where they received HD

Table 1. Baseline characteristics of patients

Variable	General care cohort (n = 156)	Critical care cohort (n = 182)	P value
Age (yr)	63 ± 16	62 ± 17	.35
Men	96 (61.5)	115 (63.1)	.84
White	133 (85.2)	163 (89.5)	.31
ESRD	115 (73.7)	89 (48.9)	<0.01
ESRD cause			
Diabetic nephropathy	60 (52.1)	31 (34.8)	0.01
Glomerulonephritis	12 (10.4)	9 (10.1)	1
Hypertension/ischemic	11 (9.5)	14 (15.7)	0.26
Cardiorenal	3 (2.6)	8 (8.9)	0.09
Polycystic kidney disease	1 (0.8)	3 (3.3)	0.44
Other	15 (13.0)	17 (19.1)	0.68
Unknown or unavailable	14 (12.1)	7 (7.8)	0.44
Comorbid conditions			
Cardiovascular disease	117 (75.0)	130 (71.4)	0.58
Diabetes	103 (66.0)	94 (51.6)	0.01
Peripheral vascular disease	90 (57.6)	94 (51.6)	0.33
Cerebrovascular disease	58 (37.1)	50 (27.4)	0.07
Malignancy	25 (16.0)	30 (16.4)	1
Charlson comorbidity index	9 (7–11)	8 (6–10)	0.02
No. of hospitalizations	2 (1–3)	2 (1–4)	0.10
Length of hospitalization (d)	5 (3–12)	12 (5–24)	<0.01
No. of HD sessions	2 (1–4)	2 (1–3)	<0.001
30-day mortality rate	31 (19.8)	40 (21.9)	0.73

ESRD, end-stage renal disease; HD, hemodialysis.
Data expressed as mean ± SD or no. (%). Charlson comorbidity index, hospitalization number, and hospitalization in days, number of HD sessions are expressed in median (interquartile range).

first. Most patients were men (n = 211; 62%) and white (n = 296; 87%). Two hundred four patients (60%) had ESRD, and 134 patients (40%) had acute kidney injury (AKI) as their primary indication for HD. ESRD as an indication for dialysis was more frequent in the general care cohort (52%), whereas AKI was more frequent in the critical care cohort (52%). Diabetes was the most common cause of ESRD (44%). Patients had a median Charlson score of 8.0 and a 30-day mortality of 21%.

In most sessions, approximately 90% of patients received conventional HD (where the session achieves both solute clearance and ultrafiltration), whereas approximately 10% received ultrafiltration only. Tunneled catheters were the most common access method (54%). Critical care patients received dialysis through temporary dialysis catheters more frequently than general care patients. Blood products were transfused in 4.5% of sessions (n = 54), distributed equally between the 2 cohorts. Characteristics of the dialysis sessions are shown in Table 2. Heparin anticoagulation of the circuit was prescribed in 54 sessions (4.5%) (Table 2). Deep venous thrombosis prophylactic subcutaneous heparin (5000−10,000 IU every 8 or 12 hours) was common (HD sessions = 546; 45%). Therapeutic systemic anticoagulation was also common (HD sessions = 412; 35%). Most received warfarin (HD sessions = 346; 30%) with or without heparin. The

Table 2. Characteristics of dialysis sessions included in this study

Variable	General care cohort ($n = 600$)	Critical care cohort ($n = 600$)	P value[a]
Hemodialysis	561 (93.5)	534 (89.0)	0.01
Diafiltration	39 (6.5)	66 (11)	0.01
Duration (min)	201 ± 36	214 ± 38	<0.01
Blood flow rate (ml/min)	350 (350−350)	350 (350−350)	<0.01
Blood flow rate (ml/min)	349 ± 44	343 ± 33	<0.01
Ultrafiltration volume (L)	1.79 ± 1.04	1.94 ± 1.2	0.02
Dialysis dose measured by Kt/V	1.45 (1.18−1.67)	1.5 (1.26−1.71)	0.4
Hemodialysis access			
Tunneled line	309 (51.5)	342 (57.0)	0.7
AV fistula	205 (34.1)	94 (15.6)	<0.01
Temporary line	68 (11.3)	146 (24.3)	<0.01
AV graft	17 (2.8)	16 (2.6)	0.9
Other	1 (0)	2 (0)	0.5
Dialyzers			
Polyflux Revaclear 300	584 (97)	575 (96)	0.8
Exeltra 190	16 (3)	25 (4)	0.8
Transfusions			
Total	27 (4.5)	27 (4.5)	1
PRBC	26 (4.3)	21 (3.5)	—
FFP	1 (0.1)	4 (0.6)	—
Platelets	0 (0.0)	2 (0.3)	—
Other	0 (0.0)	0 (0.0)	—
Concurrent antiplatelet medications			
Aspirin	262 (43.6)	357 (59.5)	<0.01
Clopidogrel	0 (0.0)	18 (0.03)	<0.01
Prophylactic anticoagulation			
Subcutaneous heparin	299 (49.8)	247 (41.1)	<0.01
Therapeutic anticoagulation	147 (24.5)	265 (44.1)	<0.01
Heparin	101 (16.8)	215 (35.8)	<0.01
Warfarin	118 (19.6)	222 (37.0)	<0.01
Combination	73 (12.1)	173 (28.8)	<0.01
Extracorporeal heparin	26 (4.3)	28 (4.6)	0.67
Laboratory data			
Hemoglobin (g/dl)	9.5 ± 1.5	8.75 ± 1.5	<0.01
Platelet (×1000/μl)	190 ± 102	206 ± 113	<0.01
International normalized ratio	1.6 ± 1.1	1.8 ± 1.0	<0.01
Albumin (g/dl)	3.2 ± 0.6	3.2 ± 0.7	0.8
CEC	30 (5.0)	33 (5.5)	0.79
Interruption of HD session	29 (4.8)	29 (4.8)	—
Loss of the HD circuit	9 (1.5)	18 (3.0)	—
Inability to return blood to patient on rinse back	3 (0.5)	3 (0.5)	—

AV, arteriovenous; CEC, clotting of extracorporeal circuit; FFP, fresh frozen plasma; ICU, intensive care unit; PRBC, packed red blood cells.
[a]P values calculated using the general estimating equation generalization of the *t*-test and χ^2 test for all the quantitative measures.
Prophylactic subcutaneous heparin dose is 5000 to 10,000 U 2 or 3 times daily.
Data are mean ± SD, no. (%), or median (interquartile range).

remainder in that group (HD sessions = 66; 5%) received therapeutic heparin. As per best practices for advanced kidney failure, no patients received low-molecular-weight heparin. Antiplatelet medication use was common (n = 619; 53%), with aspirin use in all of this subset (59.5% of the critical care and 43.6% of the general care cohorts), and a minority (<1%) also received additional antiplatelet medication. No patients received novel oral anticoagulants, because most are contraindicated in renal failure. There were higher

rates of both antiplatelet and anticoagulant medication use in the critical care cohort (Table 2).

Extracorporeal Circuit Clotting
The overall rate of CEC was 5.2% (n = 63), and rates were similar in both cohorts. Visual dialyzer circuit clotting scores correlated well with CEC ($P < 0.01$). The median total score with clotting was 7 when CEC occurred, compared with 4 when there was no CEC (Figure 3).

Determinants of CEC
Transfusions of blood products and temporary dialysis catheters were associated with higher rates of CEC (Table 3) (odds ratio [OR]: 2.4, and 2.8, respectively). Lower platelet counts and higher international normalized ratios were associated with lower rates of CEC (Table 3) (OR: 0.6 and 0.2, respectively). Hemoglobin was not a determinant for CEC (Table 3). The rate of CEC in patients who did not receive therapeutic anticoagulation was higher (n = 55; 6.9%) than that in the overall population. Antiplatelet and therapeutic systemic anticoagulant use was associated with a lower rate of CEC (OR: 0.4 and 0.2, respectively), and the effect was more pronounced in the critical care patients. There was a tendency for patients who received prophylactic anticoagulants to have lower CEC; however, our results were not significant. Lower delivered blood flow rates were associated with higher CEC rates (OR: 2.3). High ultrafiltration rates of >3 L/session were not associated with higher CEC rates (Table 3). The length of HD session was not associated with CEC rates (Table 3). Patients with AKIs had a tendency for
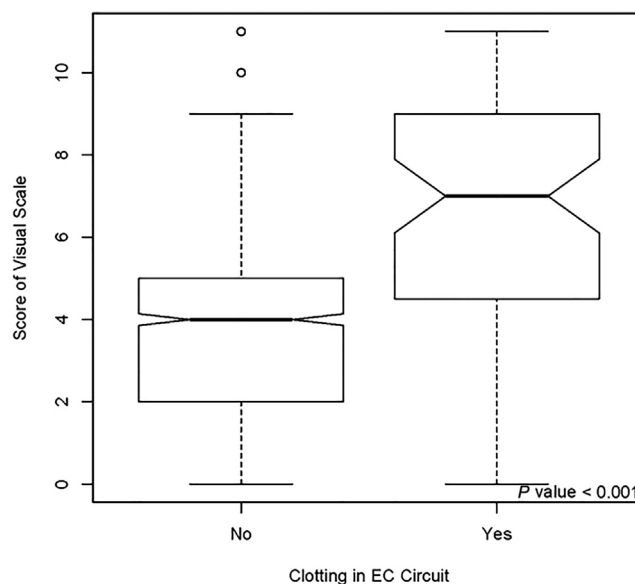

Figure 3. Clotting of the extracorporeal circuit (EC) is associated with a higher total score on the visual scale. The black bar is the median; the box width is the interquartile range.

Table 3. Determinants of clotting

Determinant	General care cohort (OR) (*P* value)	Critical care cohort (OR) (*P* value)	Overall (OR) (*P* value)
Transfusions (yes/no)	3.6 (0.02)	1.5 (0.5)	2.4 (0.04)
Access, baseline temporary line			
Tunneled line	0.2 (<0.01)	0.4 (0.02)	0.3 (<0.01)
AV fistula	0.2 (<0.01)	0.4 (0.1)	0.3 (<0.01)
AV graft	1.4 (0.6)	0 (0.9)	0.8 (0.7)
Prescription type, baseline is HD			
Diafiltration	0 (0.9)	0.3 (0.3)	0.2 (0.1)
Prescription length (h)	0.8 (0.5)	1.4 (0.2)	1.1 (0.6)
Dialyzer; baseline Revaclear 300			
Exeltra 190	2.8 (0.1)	0 (0.9)	0.9 (0.9)
Average BFR <300 (ml/min)	2.1 (0.1)	2.5 (0.05)	2.3 (0.03)
UF volume >3 L	0.4 (0.3)	0.7 (0.5)	0.6 (0.2)
Antiplatelet treatment	0.5 (0.1)	0.3 (<0.01)	0.4 (<0.01)
Systemic anticoagulation, baseline no anticoagulation			
Prophylactic	1.2 (0.6)	0.7 (0.3)	0.9 (0.7)
Therapeutic	0.3 (0.05)	0.2 (<0.01)	0.2 (<0.01)
Heparin in HD circuit	0.7 (0.7)	0 (0.9)	0.3 (0.2)
Hemoglobin <8 (g/dl)	0.7 (0.6)	0.5 (0.1)	0.6 (0.1)
Platelet <250 (×1000/μl)	0.9 (0.9)	0.4 (0.02)	0.6 (0.05)
INR >2	0.2 (0.1)	0.1 (<0.01)	0.2 (<0.01)
AKI	1.9 (0.08)	1.2 (0.5)	1.5 (0.08)

AKI, acute kidney injury; AV, arteriovenous; BFR, blood flow rate; HD, hemodialysis; INR, international normalized ratio; OR, odds ratio; UF, ultrafiltration.

more CEC events; however, the results were not significant (Table 3). When we repeated the analysis using only patients who did not receive extracorporeal heparin, all ORs agreed with those in Table 3, with the exception of arteriovenous graft, in which the ORs changed slightly but the significance did not (Supplementary Table 2).

Effect of CEC on Dialysis Efficiency
CEC was associated with a lower delivered Kt/V (difference: 0.39; $P < 0.01$).

Short-term Mortality Rate
Thirty-day mortality after hospital admission was high in both cohorts (19% and 21%, respectively) (Figure 4). Both cohorts had multiple comorbidities (median Charlson index 9 and 8, respectively).

DISCUSSION
This study demonstrated the feasibility of heparin-free HD without saline flushes in an inpatient cohort with high medical and surgical comorbidities and mortality rates. We described how this was safely implemented in a tertiary care hospital as the standard of care and identified factors associated with an increased risk of CEC (e.g., temporary dialysis catheters and blood product transfusions).
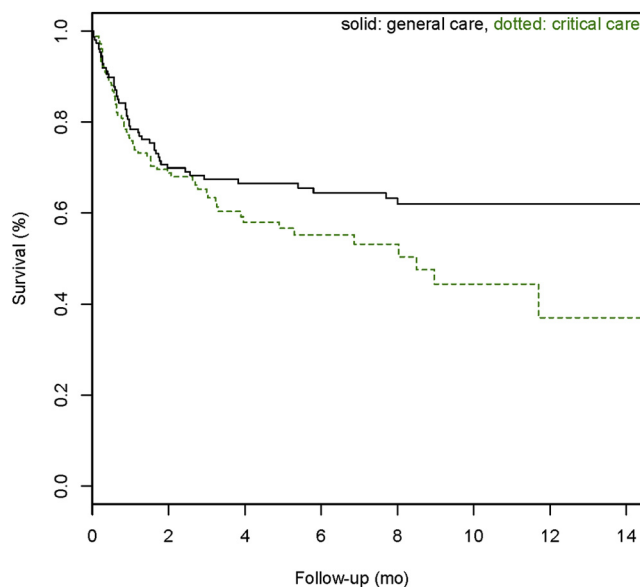
Figure 4. Kaplan-Meier survival analysis showing high short-term mortality in the cohort.

The introduction of unfractionated heparin, which prevents CEC, was key in advancing HD, preventing clotting of the dialyzer and extracorporeal tubing.[1] Unfractionated heparin remains the most commonly used anticoagulant during maintenance HD in the United States, because it is widely available at a low cost, has a relatively short half-life, and is familiar to health care practitioners.[3] However, heparin has many reported adverse effects, such as heparin-induced thrombocytopenia, hypertriglyceridemia, hyperkalemia, osteoporosis, an increased risk of catheter-related sepsis, and it has been recalled due to contamination associated with major adverse events.[3] Clearly, heparin increases the risk of bleeding. This is a major concern in ESRD patients, because they already are at an increased risk due to platelet dysfunction. Many patients are prescribed oral antiplatelet medications and anticoagulants for comorbidities, such as coronary artery disease, ischemic stroke, atrial fibrillation, and deep vein thrombosis. Adding heparin to their medication regimen further increases the risk of bleeding.[16,19] This problem is pronounced in hospitalized patients undergoing surgical procedures, in whom heparin exposure during HD could increase perioperative per procedural complication rates, leading to increased hospital lengths of stay. Others may have contraindications for anticoagulation, such as active gastrointestinal bleeding.[19,21] With dialysis tubing requiring anticoagulation, clinicians need to weigh the risk of bleeding against the risk of losing the dialyzer circuit due to clotting, resulting in dialysis dose reduction and blood loss in an anemic patient population, some of whom are anticipating future organ transplantation where avoidance of human leukocyte

antigen sensitization (following blood transfusion) is a priority.[6,7,9]

A PubMed search was performed to identify studies that examined the anticoagulation of intermittent HD circuits in the inpatient setting. Between 1995 and 2015, there were only 13 studies, most of which were retrospective, whereas >70 studies reviewed the circuit anticoagulation of continuous renal replacement therapy modalities.

In 2013, there were approximately 637,000 patients with ESRD in the United States, an increase of 3.7% since 2011.[22] United States Renal Data System data collected between 2007 and 2008, including data for incident older ESRD patients, showed that >90% received heparin during outpatient HD.[23] However, despite the potential benefits of avoiding heparin use, heparin-free HD was not associated with decreased hazards of death, bleeding, or thrombosis in patients dialyzing in the outpatient setting (90 days after starting HD).[23] Because our study addressed HD in acutely ill patients in the inpatient setting, the findings of the latter study might not be relevant. Furthermore, heparin-free HD did not compromise the dose of dialysis or require an increase in treatment time compared with standard HD in the inpatient setting in another inpatient study.[24] A study performed in an outpatient HD setting with 117 patients comparing SL tubing with Readyset (standard) bloodlines permitted a reduction in heparin dosing in 85% of patients (average −28.1%; $P < 0.001$), from 5667 to 4076 U/treatment.[13] Because of improvements in blood flow compared with standard bloodlines, staff were able to reduce flow rate and/or dialysis time yet still achieve the target Kt/V of ≥1.4 in 98.3% of patients with SL versus 77.6% with the standard bloodlines, and 10 of 18 patients with dialysis time ≥4 hours were able to reduce their treatment times by 30 minutes, Costs per treatment decreased by $3.00, mostly due to labor and dialysate savings, but also due to the reduction in hazardous waste disposal

and the heparin savings. Another study in 67 outpatient HD patients who transitioned from the Combiset lines (Fresenius Medical Care, Inc.) to SL[14] allowed a 30% reduction in the dose of heparin.[14] Heparin costs for treatment decreased by 57%, and dialyzer costs decreased by 20%. Therefore, it is reasonable to infer that inpatient heparin-free HD with SL has the potential for adding significant cost and time savings.

Our study added to the current knowledge of inpatient HD practice in a number of aspects. Our heparin-free HD protocol involved no saline flushes, yet CEC rates compared favorably with saline flush studies (Table 4). In addition to that, the rate of heparin use during dialysis at our institution signficantly decreased after transitioning to the new tubing (from 23.2% to 4%). We also implemented an objective assessment of CEC based on a visual scale, and scores correlated well with clinical CEC. Based on this experience, we recommend that CEC assessment become a standard practice for inpatient HD. We also identified factors that could lead to an increased risk of CEC (temporary dialysis catheters and blood product transfusions), and although implementing a saline flushing protocol in all patients across the practice is difficult and resource intensive, implementing such a protocol in a subgroup of patients that is at high risk of CEC is reasonable. In our inpatient units, despite the availability of a saline flush protocol, it is rarely used (probably due to the extra nursing time and other resources required).

We noticed a tendency for CEC during transfusions when blood products were given through the EC. However, the number of occurrences were too small to afford reasonable power for comparison, and further study is needed.

One surprising finding in this study was the high prevalence of aspirin (43%) and warfarin (19%) use, especially in the critical care setting. Although these were associated with lower CEC rates, it is important to keep in mind that these medications, especially in

Table 4. A comparison of our study with various heparin-free saline flush protocols

Author/reference	Design	Population	Year	BFR (ml/min)	Average UF (L/session or L/h) (mean ± SD)	Saline flush regimen	Clotting of the EC (%)
This study (n = 1200)	Prospective	Inpatient, ESRD and AKI	2014	350	1.87 ± 1.12 L/session	None	5
Sahota[25] (n = 400)	Retrospective	Inpatient, ESRD and AKI	2013	>350	1 ± 0.817 L/session in treatments that clotted versus 2 ± 1.366 L/session in those that did not	100 ml q15 min	1
Stamatiadis[26] (n = 1224)	Retrospective	Inpatient, ESRD and AKI	2004	<250	0.891 ± 0.971 L/session	50 ml q60 min	5
Schwab[5] (n = 262)	Prospective	Inpatient, mostly ICU, strictly AKI	1987	300	1.36 ± 0.003 L/h	50−100 ml q15 min	2[a]
Sanders[6] (n = 158)	Retrospective	Inpatient, in kidney transplant recipients (perioperative and postoperative), ESRD and AKI	1985	300	Not provided	100 ml q30 min	5 complete 6 partial
Casati[7] (n = 111)	Prospective	Inpatient, mostly post-transplant AKI, but some ESRD	1983	300	Not provided	250−300 ml q15 min	10

AKI, acute kidney injury; EC, extracorporeal circuit; ESRD, end-stage renal disease; ICU, intensive care unit.
[a]Heparin was administered when early clotting of the EC was detected.

combination, put patients at a higher bleeding risk (incidence of 6.3% per person-year[16]). Furthermore, a minority of HD runs (4.5%) required extracorporeal heparin, which was determined by the ordering dialysis provider.

It is worthwhile to point out the high mortality in this group (30-day mortality of approximately 20%) (Figure 4). This is in line with other data that show poor outcomes in hospitalized dialysis patients and those with acute kidney failure who require dialysis initiation. These data support the recommendation of advanced directive conversations and palliative care as important steps in caring for these patients. Further research should be conducted to identify measures that could improve outcomes.

There were several limitations to our study: (i) lack of a control group (this was not feasible due to patient safety concerns); and (ii) a high prevalence of concurrent systemic anticoagulant use in our inpatient population. It is worthwhile to point out that before transitioning to air-free dialysis tubing with the heparin-free protocol, the rates of heparin use and CEC were 23.2% and 10.8%, respectively. It was also our center experience (although subjective) that cutting dialysis sessions short due to clotting of EC was less frequent than in the past.[27] We attempted to compare the CEC rate to other reported data; however, there were difficulties in making these comparisons. First, the literature was scant and spanned 3 decades, during which time many technological advances in HD circuits and equipment occurred. Second, most reported data were retrospective, and CEC rates might have been underestimated. Third, transfusion rates in hospitalized dialysis patients decreased over time, as has erythropoietin dosing. Fourth, the definition of CEC varied by institution and implemented protocols.

Although the Kidney Disease Outcomes Quality Initiative recommends continuous monitoring of processes relating to dialysis delivery, delivery of inpatient HD in acutely ill patients has received little attention, and no clinical performance measures or guidelines currently exist. This was the first contemporary prospective study to examine CEC in an inpatient setting. It revealed, that with current acute inpatient practice, heparin during HD is no longer routinely required. Our heparin-free protocol was safe and effective, and CEC rates were low. Use of temporary catheters and blood product transfusions were potential risk factors, and further studies exploring methods to decrease CEC in these instances are needed.

DISCLOSURE

SUPPLEMENTARY MATERIAL

Table S1. Visual assessment grading of extracorporeal circuit clotting.
Table S2. Determinants of clotting in patients who did not receive extracorporeal heparin during dialysis.
Document S1. Study Protocol, which includes the post-rinseback visual scale (From Medisystems: A NxStage Company. Post-rinseback visual scale. Lawrence, MA: NxStage. 2014. Used with permission. Copyright © 2014 NxStage Medical, Inc., Medisystems, ReadySet and Streamline are registered trademarks of NxStage Medical, Inc. Dialog+ is a registered trademark of B. Braun Medical Inc. Fresenius and 2008 are trademarks of Fresenius Medical Care Holdings, Inc. or its affiliated companies. Caution: Federal law restricts this device to sale by or on the order of a physician. APM552 Rev. B). This document is not intended to replace Streamline Instructions for use and does not include all of the information necessary to use the products safely and effectively. Product users should review and refer to the Instructions for Use for complete use information, including all warnings and precautions. Medisystems and Streamline are registered trademarks of NxStage Medical, Inc. Caution: Federal law restricts this device to sale by or on the order of a physician. TM0434 Rev. B.

Document S2. Dialysis tubing priming and setup procedures.

Supplementary material is linked to the online version of the paper at www.kireports.org.

REFERENCES

1. Davenport A. What are the anticoagulation options for intermittent hemodialysis? *Nat Rev Nephrol*. 2011;7:499–508.

2. Ludlow MK. Heparin-free dialysis. *ANNA J*. 1989;16:295–298.

3. Shen JI, Winkelmayer WC. Use and safety of unfractionated heparin for anticoagulation during maintenance hemodialysis. *Am J Kidney Dis*. 2012;60:473–486.

4. Rottembourg J, Bouayed F, Durande J, El Shahat Y, Guimont MC. No heparin for routine hemodialysis sessions in patients with high bleeding risk. *Artif Organs*. 1979;3, 311–311.

5. Schwab SJ, Onorato JJ, Sharar LR, et al. Hemodialysis without anticoagulation: one-year prospective trial in hospitalized patients at risk for bleeding. *Am J Med*. 1987;83:405–410.

6. Sanders PW, Taylor H, Curtis JJ. Hemodialysis without anticoagulation. *Am J Kidney Dis*. 1985;5:32–35.

7. Casati S, Moia M, Graziani G, et al. Hemodialysis without anticoagulants: efficiency and hemostatic aspects. *Clin Nephrol*. 1984;21:102–105.

8. Caruana RJ, Raja RM, Bush JV, et al. Heparin free dialysis: comparative data and results in high risk patients. *Kidney Int*. 1987;31:1351–1355.

9. Keller F, Seemann J, Preuschof L, et al. Risk factors of system clotting in heparin-free haemodialysis. *Nephrol Dial Transplant*. 1990;5:802–807.

10. Cronin RE, Reilly RF. Unfractionated heparin for hemodialysis: still the best option. *Semin Dial*. 2010;23:510–515.

11. Laville M, Dorval M, Fort Ros J, et al. Results of the HepZero study comparing heparin-grafted membrane and standard care show that heparin-grafted dialyzer is safe and easy to use for heparin-free dialysis. *Kidney Int*. 2014;86:1260–1267.

12. NxStage Medical: Streamline website. Available at: http://www.nxstage.com/hcp/products/streamline/. Accessed April 5, 2017.

13. Cooke JD, Moran J. Streamline airless system optimizes dialysis adequacy with reduced costs. Available at: https://www.asn-online.org/api/download/?file=/education/kidneyweek/archives/2007-abstracts-archive.pdf. Accessed April 5, 2017.

14. Hass S, Ahuja M. Improving adequacy, heparin anticoagulation and dialyzer efficiency with new bloodline technology. Available at: https://www.asn-online.org/api/download/?file=/education/kidneyweek/archives/RW10Abstracts.pdf. Accessed April 5, 2017.

15. Smith P. Streamline bloodlines improve Kt/V while lowering dialysate usage. *Adv Chronic Kidney Dis*. 2010;17:209.

16. Holden RM, Harman GJ, Wang M, et al. Major bleeding in hemodialysis patients. *Clin J Am Soc Nephrol*. 2008;3:105–110.

17. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. 2005;43:1130–1139.

18. Fresenius Medical Care. *2008K Hemodialysis Machine Operator's Manual*. Concord, CA: Fresenius USA, Inc.; 2015:104–111.

19. Kuhlmann U, Goldau R, Samadi N, et al. Accuracy and safety of online clearance monitoring based on conductivity variation. *Nephrol Dial Transplant*. 2001;16:1053–1058.

20. McIntyre CW, Lambie SH, Taal MW, et al. Assessment of haemodialysis adequacy by ionic dialysance: intra-patient variability of delivered treatment. *Nephrol Dial Transplant*. 2003;18:559–562.

21. Pinson CW, Schuman ES, Gross GF, et al. Surgery in long-term dialysis patients: experience with more than 300 cases. *Am J Surg*. 1986;151:567–571.

22. US Renal Data System. *2014 Annual Data Report: Epidemiology of Kidney Disease in the United States. ESRD in the United States: An Overview of USRDS Annual Data Report Volume 2*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2014:S79–S92.

23. Shen JI, Mitani AA, Chang TI, et al. Use and safety of heparin-free maintenance hemodialysis in the USA. *Nephrol Dial Transplant*. 2013;28:1589–1602.

24. McGill RL, Blas A, Bialkin S, et al. Clinical consequences of heparin-free hemodialysis. *Hemodial Int*. 2005;9:393–398.

25. Sahota S, Rodby R. Inpatient hemodialysis without anticoagulation in adults. *Clin Kidney J*. 2014;7:552–556.

26. Stamatiadis D, Helioti H, Mansour M, et al. Hemodialysis for patients bleeding or at risk for bleeding, can be simple, safe and efficient. *Clin Nephrol*. 2004;62:29–34.

27. Semret M, Ryan M, Albright R, et al. A quality audit analysis of hemodialysis circuit clotting in an inpatient dialysis unit. Available at: https://www.asn-online.org/api/download/?file=/education/kidneyweek/archives/KW11Abstracts.pdf. Accessed January 24, 2017.