Title:

Locking hemodialysis catheters with Trimethoprim-Ethanol-Ca-EDTA to prevent bloodstream infections. A randomized, evaluator blinded clinical trial.

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Summary:

Central line associated bloodstream infections(CLABSI) often result from intraluminal microbial colonization and are associated with morbidity, mortality, and substantial costs. In patients on chronic hemodialysis, a trimethoprim, ethanol and Ca-EDTA Lock solution significantly reduced the incidence of CLABSI.

Abstract:

Background: Central line associated bloodstream infections(CLABSI) often result from intraluminal microbial colonization and are associated with morbidity, mortality, and substantial costs. The use of antimicrobial catheter lock solutions may reduce the incidence of CLABSI. ***Methods:*** Patients undergoing hemodialysis through a prevalent central venous catheter(CVC) were randomly assigned to have their CVC locked between dialysis sessions with an antimicrobial catheter lock solution containing trimethoprim 5 mg/mL, Ethanol 25% and Ca-EDTA 3%(Investigational Medical Device, IMD) or heparin 5,000 U/mL(Active Control Heparin, ACH). Exit site care was standardized by protocol-driven use of skin antiseptics and occlusive dressings. The composite primary endpoint consisted of the incidence of CLABSI and the use of intra-catheter thrombolytic treatment(TT). Given the viscosity and odor of the IMD, blinding was impossible. Therefore, the incidence of CLABSI was adjudicated by a blinded endpoint committee. ***Results:*** 270 patients on hemodialysis were enrolled and followed for a total of 43,738 CVC days. Despite the low CLABSI incidence of 0.41/1,000 CVC days in patients randomized to ACH, the IMD further reduced the incidence 4.56-fold to 0.09/1,000 CVC days($P<0.03$). The product was well tolerated, and the frequency and severity of adverse events were comparable between groups. Intracatheter instillation of thrombolytics was more frequent in patients receiving the IMD (12% ACH, 40% IMD;$P<0.001$) but rates of catheter removal did not differ(13% in ACH and 11% in IMD). Overall dialysis adequacy was comparable between groups. **Conclusions:** In patients on chronic hemodialysis, a trimethoprim, ethanol and Ca-EDTA Lock solution significantly reduced the incidence of CLABSI.

Key words:

central line associated blood stream infection (CLABSI); antimicrobial catheter lock; hemodialysis; randomized trial; biofilm

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Introduction

In certain patient populations, central venous catheters (CVCs) may be needed for months or even years to enable immediate, reliable and effective vascular access without the need for repeat venipuncture[1]. Between use, all CVCs must be filled with an aqueous lock solution to create a hydrostatic barrier to prevent the retrograde flow of blood into the device and to maintain CVC patency. Saline and/or heparin containing lock solutions allow microbial colonization within catheter lumens that can result in life-threatening blood stream infections. Although heparin is used to maintain catheter patency due to its potent anticoagulant activity, as a polysaccharide it has no intrinsic antimicrobial activity[2] and may actually support microbial growth[3].

Infectious complications remain a significant problem for patients requiring long-term vascular access. The use of a CVC in hemodialysis (HD) patients is a major risk factor for development of bacteremia and death with hazard ratios of 5.4 and 2.8 respectively[4] and central line associated blood stream infections(CLABSIs) are reported to account for 48% to 73% of all cases of bacteremia in HD[5]. Furthermore, after cardiovascular disease, infection is the second leading cause of death in hemodialysis patients[6]. In addition to the medical risks associated with blood stream infections the mean incremental cost to treat CLABSI in HD patients is estimated to be $17,000-32,000 USD[7]

The incidence of CLABSI may vary substantially between centers based on hygiene practice and the type of lock solution used. But even in HD centers with a low overall incidence (e.g.

<0.5/1,000 catheter days), the lifetime risk for the individual CVC dependent patient remains substantial[8].

The objective of this study was to evaluate in a randomized trial, the incidence of CLABSI and the frequency of thrombolytic treatment(TT) which was used as a proxy endpoint for catheter patency in patients, whose CVCs were locked with either an antimicrobial catheter lock solution containing trimethoprim, ethyl alcohol, and Ca-EDTA (PrevaCept Lock Solution, the investigational medical device(IMD)) or active control heparin(ACH) as the standard of care. In addition, dialysis adequacy was compared between the groups.

Study Subjects, Materials and Methods

This was a multicenter, prospective, 1:1 randomized, open-label, evaluator-blinded, active-controlled study of the IMD compared against active control heparin (ACH, 5000U/ml) containing benzyl alcohol 0.9% as a preservative supplied in 5 mL vials. The IMD was an antimicrobial catheter lock solution containing trimethoprim (5 mg/mL), ethanol (25% by volume) and edetate calcium disodium (3% by weight) in a clear sterile phosphate buffered saline solution of pH 8.5 containing glycerol and propylene glycol as stabilizers, supplied in 10 mL clear glass vials. Patients aged 18-85 receiving hemodialysis via prevalent tunneled double lumen or two separate direct central polyurethane venous catheters were included if they were expected to receive dialysis for a minimum of 45 days after study enrollment (detailed inclusion exclusion criteria are provided in online supplement). Diagnosis of CLABSI was made by independent clinical endpoint committee(CEC) members who were blinded to treatment group

assignments and adjudicated culture confirmed blood stream infections to determine which met the CLABSI criteria[9] and reviewed the appropriateness of the use of TT for the final statistical analysis. The CEC was comprised of two nephrologists and one infectious disease physician with extensive experience in the management of hemodialysis patients and/or the diagnosis and management of patients with CLABSI.

The incidence of CLABSI was compared using two-sided Fisher's exact test. The incidence of (TT) was analyzed to test for non-inferiority by constructing a four-fold table of treatment by the number of patients receiving TT. A 95% confidence interval (CI) was constructed for the relative risk (RR). Flow parameters, URR and Kt/V were assessed using analysis of covariance (ANCOVA). A more detailed explanation of the clinical trial methodology and CLABSI endpoint is available as an online supplement.

Results

Study Population and Baseline Characteristics

The study assessed 282 subjects for eligibility of whom 12 were deemed ineligible or refused to participate in the study; the remaining 270 were randomized (Figure 1). All randomized patients are included in the intent to treat (ITT) analysis while only those who also received at least one instillation of IMD or ACH were included in the Safety Population (140 IMD patients, 130 ACH patients). The safety and ITT populations were the same.

Treatment groups were well balanced regarding all demographic and baseline characteristics (Table 1) including the stratification factors. The number of patient CVC-days of exposure was

22,178 in the ACH group and 21,560 in the IMD group (p=n.s). The median follow-up was 177 days in ACH and 175 days in IMD. There were 112 patients enrolled in Hungary (55 ACH and 57 IMD) and 158 patients enrolled in Poland (75 ACH and 83 IMD).

The study was initiated on 18 July 2012 and closed on 31 October 2014. The last study assessment for the 30-day follow up was on 30, November 2014. This report presents the results on data from all 270 patients enrolled. An interim analysis was conducted on 27 October 2014 to determine whether to expand to 400 patients or stop for futility. The DMC evaluated safety and the two coprimary endpoints: the incidence of CLABSI, and the use of TT as a proxy for catheter patency. Following the interim analysis, the study was halted for futility in meeting the co-primary endpoint for TT use.

CLABSI Outcomes

All culture confirmed, blood stream infections were adjudicated by the Clinical Endpoint Committee and are presented in Table 2. Patients randomized to IMD had a 4.5-fold lower risk of CLABSI infection (P=0.03, two-sided Fisher's Exact Test) compared to patients randomized to ACH. CLABSI infections were balanced between countries, with 6 events occurring in Hungary and 5 in Poland. When incorporating the protocol stratification factors of catheter type (tunneled versus direct catheter), catheter age, or country, IMD was superior to ACH (Table 2). Time to first documented CLABSI was statistically different between groups (log rank test, P=0.03) with IMD patients having a significantly longer CLABSI free period. Based on a 6-month

median treatment duration, the number needed to treat (NNT) to prevent one CLABSI event is 18 subjects.

Microbial pathogens isolated from blood cultures from patients diagnosed with CLABSI are presented in Table 3. Patients with blood stream infections adjudicated as not having originated from the CVC were balanced between treatment groups with 4 (3%) in ACH versus 3 (2%) in IMD (p=0.71).

The rate of overall infections and antibiotic use was also evaluated. The ACH group experienced a greater incidence of overall infections (44% ACH vs 36% IMD) and serious device-related infections (5% ACH vs 2% IMD). The use of antibiotics for systemic use, a secondary metric of clinically significant infections, also occurred at a higher incidence in the ACH group (44% ACH vs 31% IMD) although the difference was not statistically significant. The number of patients hospitalized due to infection was greater in ACH (20 ACH vs 13 IMD) and the mean number of hospitalization days due to infection was 300 in ACH compared to 221 in the IMD group.

TT Outcomes

The protocol-defined co-primary endpoint of thrombolytic treatment (TT) use was intended as a proxy measure for CVC flow rate maintenance. Thrombolytics were used more frequently in patients in the IMD group (12% ACH, 40% IMD; P<0.001) (Table 4). In patients with Split-D catheters >13.5 French, the difference between groups in TT use was smaller (17% ACH vs 33% IMD, P=0.03, Fisher's exact test) compared to patients with 10 French Tesio catheters or 11.5 French coaxial catheters where the difference in TT use between groups was greater (2% ACH

vs 52% IMD, P<0.001 Fisher's exact test). Although the protocol provided guidelines to standardize use of TT, it was noted that most of the use was due to "the discretion of the investigator," which was permitted in the protocol. Lock solution failure due to occlusive malfunction as defined by the protocol and confirmed by the clinical endpoint committee occurred in 2 (1.5%) in ACH versus 7 (5%) in IMD, the difference was not significant. Occlusive malfunction was reported as the reason for catheter removal in a single patient in the IMD group.

Patients with polyurethane central venous catheters of various types, sizes and manufacturers were allowed to be enrolled in the study. A review of catheter types by country indicated that 70% of catheters used in Hungary were 10 French Tesio and 13% were 11.5 French Coaxial type, whereas over 99% of catheters used in Poland were 13.5-15.5 French Split-D type catheters.

Safety analyses were performed by catheter size, by country and by TT use; no clinically or statistically meaningful changes in AEs, deaths or SAEs were observed between the treatment groups. The increased use of TT was not associated with higher rates of catheter removal with 17 (13%) in ACH and 16 (11%) in IMD(Table 4). Transition to alternative access such as fistula or peritoneal dialysis was the most common reason for catheter removal as expected in this patient population.

Flow Metrics and Kt/V

Flow metric data was prospectively obtained directly from dialysis machines for 18,771 dialysis sessions (9,518, ACH and 9253 IMD) during the course of the study and included: total blood

volume processed (TBVP), blood flow rates, duration of dialysis session, pressure parameters, and dialysis adequacy as assessed by Kt/V and URR (Table 5). Flow metrics take into account the effect of the study lock solution on maintaining catheter patency as well as potential effects of the use of TT. The mean total blood volume processed (TBVP) was 73.0 L in ACH compared to 71.0 L in IMD, a 2.7% difference between treatment groups ($p<0.001$).

Kt/V and URR (%) were measured monthly for all patients and mean values were calculated during the treatment period. The mean Kt/V value for IMD was approximately 97% of ACH and the mean URR (%) for IMD was approximately 97% of ACH (Table 5); these differences were not statistically significant. The overall TBVP and flow rates were within the clinically recommended and accepted values for adequate dialysis. In addition, regardless of treatment group or catheter size, flow through the catheters was sufficient to achieve adequate dialysis as assessed by standard measures of Kt/V and URR (%), which were well above acceptable thresholds[10]; (Hemodialysis Adequacy Work Group 2006).

Safety

Safety parameters including adverse events (AEs), serious adverse events (SAEs) and deaths are reported in Table 6. Given the long follow-up time and the population being studied the incidence of (S)AE was high. Six percent of ACH patients and 9% of IMD patients died during the treatment period or within the 30-day safety follow-up period (Table 6). All patient deaths were assessed by the investigator, study medical monitor, and CEC as not related to study treatment. Serious Adverse Events (SAEs) were reported in 38% of ACH patients and 31% of IMD patients.

Overall AEs were similar between groups with (82%) of ACH and (75%) of IMD patients who experienced at least one AE, with similar proportions of patients experiencing moderate AEs (45% ACH vs 41% IMD) and severe AEs (25% ACH vs 24% IMD). The overall safety profile did not reveal any safety signals or clinically significant differences between the IMD and ACH groups nor amongst any of the sub-groups (by country, by catheter use, or by TT use) that were analyzed.

Concomitant medications were, in general, similar in both groups with the following notable exceptions where there was a difference of over 10% between groups: diuretics 76 (58%) ACH vs 60 (43%) IMD and antibacterials for systemic use 57 (44%) ACH vs 43 (31%) IMD. Other medications used to manage end-stage renal disease patients and their comorbid conditions were generally similar between the two treatment groups.

No significant differences in mean values of hematology parameter over time were observed in either group. A subset of subjects in ACH had increased partial thromboplastin time (45% ACH vs 17% IMD) and a subset of subjects in the IMD group (18%) had reductions in reported magnesium levels. Both outcomes were attributed to phlebotomy procedures resulting in the incomplete removal of lock solution before blood collection, as heparin is known to prolong clotting time and EDTA is known to confound magnesium assays. No additional clinically meaningful differences in chemistry or hematology were observed.

Discussion

In this RCT, patients randomized to IMD had a remarkable 4.5-fold lower risk of CLABSI

infection compared to those randomized to ACH (0.41/1,000 vs 0.09/1,000 catheter-days, respectively; P=0.03). Protocol-driven standardization of exit site care with the use of chlorhexidine/alcohol-based skin antiseptics and occlusive dressings, as well as strict adherence to hand hygiene and sterile technique likely accounts for the exceptionally low rate of infection in the control arm. Nevertheless, despite the low rate observed in the ACH control group, IMD achieved a further, statistically significant reduction in blood stream infections. To put this into perspective, the observed IMD CLABSI rate of 0.09/1,000 catheter-days (0.27/100 patient-months) is equivalent to one event for every 30-years of patient treatment. The incidence of CLABSI in the IMD group was similar to the National Healthcare Safety Network (NHSN) reported incidence of blood stream infections in dialysis patients in the United States using arterio-venous fistulas (AVF) for vascular access (0.26/100 patient-months) and 8-fold lower than in patients using CVCs (2.16/100 patient-months) in calendar year 2014, approximately contemporaneous with our study[11].

In this study CLABSI was adjudicated by an independent CEC based on pre-defined criteria namely clinical signs and symptoms of infection, no other more likely primary source of infection and growth of the same organism from blood drawn from the arterial or venous CVC hubs or peripheral venipuncture when feasible. These criteria are aligned with recent recommendations published in 2018 regarding trial endpoints for dialysis catheters[12].

With respect to other antimicrobial lock solutions, several review articles have shown clinical benefits of “active agent” lock solutions in reducing rates of CLABSI. Gentamicin locks were shown to significantly reduce the incidence of CLABSI in a meta-analysis of 18 studies and 2395

hemodialysis patients[13]. Citrate locks in concentrations of 30 or 47% were studied in 3 randomized trials with a total of 987 patients and showed mixed results with a positive, neutral as well as negative impact on the incidence of CLABSI[14-16]. Taurolidine-citrate locks reduced CLABSI (relative risk = 0.47, 95% CI: 0.25-0.89) in a meta-analysis of 3 randomized trials involving 236 patients (both HD and non-HD patients)[17]. The effect was significant for Gram-negative but not for Gram-positive infections. Finally, citrate-methylene blue-methylparaben-propylparaben lock (CMB), minocycline-EDTA and ethanol 70%/heparin locks were each studied in a single randomized trial. CMB lock significantly reduced CLABSI from 0.8 to 0.2/1,000 days in 403 hemodialysis patients[18] while Minocycline-EDTA significantly reduced CLABSI from 4.3 to 1.1/1,000 days in 204 hemodialysis patients[19]. The ethanol/heparin lock decreased the incidence of CLABSI from 6.7 to 2.5/1,000 days in 103 hemodialysis patients[20].

However, a remaining concern of antibiotic locks without ethanol is the potential for emergence of antibiotic resistance[21]. For example, an *in vitro* analysis of Gentamicin, Oxacillin and Vancomycin as lock solutions, even at very high pharmacological concentrations (1,0000, 5,000 and 5,000 ug/ml, respectively) failed to sterilize the biofilms of many coagulase negative staphylococcus strains[22]. Hence, the lock solution used in the current study that reduced the incidence of CLABSI has also been shown to sterilize biofilms of Gram-positive, Gram-negative bacteria and fungal pathogens *in vitro*[23].

In this trial, there were three issues that complicated our ability to assess the effect of the IMD on catheter patency. The first challenge is that there is no standardized objective metric for "patency". The use of thrombolytic treatments (TT) was chosen as a proxy measure for catheter patency. However, physician discretion for the use of TT was allowed by the protocol which was

confounded by a second challenge in that study sites were not blinded to the lock solutions being used, due to the discernable differences in heparin solution compared to IMD which contains ethanol. Finally, Actilyse was available as study material free of charge and in unlimited supply. These factors combined may partially explain the increased TT utilization in the study.

Although in this clinical trial there was greater use of TT with IMD (7.3/1,000 catheter-days) as compared to ACH (1.5/1,000 catheter-days) the absolute rate is comparable to thrombolytic use associated with other lock solutions (2.7-11/1,000 CVC days)[24],[15],[25] and with heparin 1,000 U/mL (10.31/1,000 catheter-days). It is noted that the utilization of TT was greater in Tesio 10F and coaxial 11.5F catheters compared to Split-D catheters 13.5F and greater, thus when possible the use of a Split-D catheter 13.5F or larger is suggested when locking with IMD in hemodialysis patients.

Finally, the role of the catheter is to provide vascular access for adequate dialysis. In this respect, all measures of dialysis efficacy (TBVP, URR and Kt/V) were found to be well within accepted guidelines for both groups of patients and rates of catheter removal were similar between groups. Hence, we conclude that although TT use was greater in the IMD group than in the ACH group, there were no clinically meaningful differences between groups in terms of adequacy of dialysis.

The cost-effectiveness of a preventive intervention depends on the baseline incidence, the quality of life of the population and the morbidity and mortality of the disease prevented.

Although a detailed cost-effectiveness analysis is beyond the scope of this paper, potential cost-savings with the use of IMD may be substantial given that CLABSI associated treatment costs $17,000–32,000 USD[7]. Indeed, using $17,000 per CLABSI and a low incidence of 0.4/1,000 days in ACH and considering that 1 additional TT was used every 200 catheter days, the observed 75% reduction in CLABSI extrapolates to an annual cost savings of $130,000 per every 100 HD patients treated.

In conclusion, the ability of IMD to reduce CLABSI to 0.09/1,000 catheter-days, a rate most commonly associated with arteriovenous fistula is a significant finding that has potential to substantially improve outcomes and treatment options for HD patients. If borne out in broader clinical practice, the use of IMD would have a major impact on the health, well-being and cost of treating patients requiring long-term CVC use.

Acknowledgements

Registration number of trial registry

The study was conducted according to the guidelines of International Standards Organization (ISO) 14155:2011 “Clinical investigation of medical devices for human subjects – Good clinical practice” and was conducted in full compliance with the World Medical Association Declaration of Helsinki.

Conflict of Interest Statement

John Cheronis, Gino DiSciullo, Krzysztof Appelt, Roger Aitchison and Gilad Gordon were employed by or were independent contractors for Prevacept Infection Control, Inc. (formerly known as Great Lakes Pharmaceuticals, Inc.). Bolesław Rutkowski Professor at Uniwersyteckie Centrum Kliniczne, Klinika Nefrologii in Gdansk, Poland was country principal investigator for Poland and Botond Csiky, M.D. of FMC Dialízis Központ Pécs in Pecs, Hungary was the country principal investigator for Hungary.

Professors Michel Jadoul, Bart Rijnders, Richard Fluck served as an independent clinical endpoint committee members and were blinded to treatment group assignment throughout the conduct of the study. BJA Rijnders, M Jadoul and R Fluck were reimbursed for out of pocket and travel related expenses and paid for their work as members of the CEC in this trial.

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Figure 1. Trial Flow Diagram

Table 1. Baseline Characteristics of patients

Characteristic	ACH (N=130)	IMD (N=140)	Total (N=270)
Patient			
Median Age (yrs)	67.0	65.5	66.0
Male, n (%)	59 (45)	62 (44)	121 (45)
Female, n (%)	71 (55)	78 (56)	149 (55)
Median weight (kg)	70.95	70.75	70.85
Median height (cm)	163.5	165.0	164.0
White, n (%)	130 (100)	140 (100)	270 (100)
Age (category (n %)			
<50	19 (15)	20 (14)	39 (14)
50-65	40 (31)	50 (36)	90 (33)
>65	71 (55)	70 (50)	141 (52)
Cause of Renal Failure (n %)			
Cystic/Hereditary/Congenital Diseases	17 (13)	14 (10)	31 (11)
Diabetes	39 (30)	37 (26)	76 (28)

Characteristic	ACH (N=130)	IMD (N=140)	Total (N=270)
Glomerulonephritis	10 (8)	13 (9)	23 (9)
Hypertension/Large Vessel Disease	27 (21)	26 (19)	53 (20)
Interstitial Nephritis/Pyelonephritis	17 (13)	17 (12)	34 (13)
Other	20 (15)	33 (23)	53 (20)
Country (n %)			
Hungary	55 (42)	57 (41)	112 (41)
Poland	75 (58)	83 (59)	158 (59)
Catheter Type (n %)			
Direct	11 (8)	13 (9)	24 (9)
Tunneled	119 (92)	127 (91)	246 (91)
History of catheter occlusion within 18 months prior to Screening (n %)	16 (12)	21 (15)	37 (14)
Thrombolytic use within 18 months prior to Screening (n %)	81 (62)	101 (72)	182 (67)

Characteristic	ACH (N=130)	IMD (N=140)	Total (N=270)
Blood stream infection within 18 months prior to Screening (n %)	6 (5)	16 (11)	22 (8)
Median months since catheter insertion	5.4	5.6	5.5

Note: There were no statistical differences in baseline characteristics between treatment groups

Table 2: Summary of CLABSI Events

Characteristic	ACH (N=130)	IMD (N=140)
Patients with CLABSI	9 (6.9%)	2 (1.4%)
Incidence per 1,000 cvc days	0.41	0.09
Fisher's Exact Test (2-tailed) p-value	0.03	
Catheter Type: Direct	0 (0%)	0 (0%)
Catheter Type: Tunneled	9 (7%)	2 (1%)
CMH p-value	0.023	
Catheter Age <=30days	1 (7%)	0 (0%)
Catheter Age >30days	8 (6%)	2 (1%)
CMH p-value	0.024	
Country: Hungary	5/55 (9%)	1/57 (2%)
Country: Poland	4/75 (5%)	1/83 (1%)

Table 3. Microorganisms cultured from CLABSI patients

Group	Patient No	Country	Days to CLABSI	Organism
IMD Group				
	107-011	HU	257	*S. aureus*
	210-003	PO	16	*Staphylococcus hominis, Streptococcus anginosus*
ACH Group				
	101-020	HU	55	*S. aureus*
	103-002	HU	47	*Kocuria*
	104-004	HU	145	*Proteus mirabilis*
	107-012	HU	140	*Escherichia coli*
	110-004	HU	22	*Klebsiella pneumoniae*
	202-024	PO	56	*S. aureus*
	205-003	PO	173	*S. aureus*
	212-002	PO	30	*Staphylococcus hemolyticus*

216-002	PO	7	*S. aureus*

Table 4: Thrombolytic Treatments and removal of CVCs

Characteristic	ACH (N=130)	IMD (N=140)	P-value

Characteristic	ACH (N=130)	IMD (N=140)	P-value
Patients with Thrombolytic Treatment	15 (12%)	56 (40%)	<0.001
TT use per 1,000 CVC days	1.5	7.3	
TT use by catheter type			
10 Fr Tesio & 11.5 Fr coaxial catheters	1/48 (2%)	27/52 (52%)	<0.001
>13.5 Fr Split D Catheters	14/82 (17%)	29/88 (33%)	0.02
TT use by country			
Hungary	1/55 (2%)	27/57 (47%)	<0.001
Poland	14/75 (19%)	29/83 (35%)	0.03
Patients with a Catheter Removed	17 (13%)	16 (11%)	0.72

Table 5: Mean Dialysis Duration, Flow Rate and Total Blood Volume Processed

Time Point	Endpoint	IMD	ACH	Difference (95% CI)	% Difference	P-value
All	Total Blood Volume Processed (Liters)	71.0	73.0	-2.0 (-2.9,-1.1)	2.7%	<0.001
	Duration of Dialysis (min)	245.5	245.4	0.1 (-1.2,1.5)	0.0%	0.845
	Pre-Pump Arterial Line Pressures (mmHg)	-186.4	-178.5	-7.9 (-22.4,6.5)	4.2%	0.281
	Mean Flow Rate (mL/min)	288.2	299.5	-11.3 (-16.3,-6.3)	3.8%	<0.001
	KT/V	1.50	1.55	-0.05 (-0.13,0.03)	3.2%	0.252
	URR (%)	73.5	75.8	-2.4 (-5.5,0.8)	3.2%	0.140

Table 6: Safety Summary

	ACH (N=130)	IMD (N=140)	Total (N=270)
Patients with at least one AE	82%	75%	211 (78)
AEs by system organ class >5% difference between groups			
Infections	44%	36%	
Gastrointestinal disorders	19%	26%	
Respiratory, thoracic and mediastinal disorders	4%	10%	
Deaths	6%	9%	
AEs leading to death			
Infections	2%	3%	
Cardiac disorders	2%	2%	
General disorders and administration site conditions	2%	3%	
Nervous system disorders	0%	1%	
Patients with at least one SAE	38%	31%	34%

	ACH (N=130)	IMD (N=140)	Total (N=270)
SAEs ≥2% difference between groups			
Infections	18%	11%	
Cardiac disorders	5%	7%	
General disorders and administration site conditions	3%	6%	
Gastrointestinal disorders	2%	5%	

Figure 1. Trial Flow Diagram