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Taurolidine/Heparin Lock Solution and Catheter-Related Bloodstream Infection in Hemodialysis

A Randomized, Double-Blind, Active-Control, Phase 3 Study

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Abstract

Background Catheter-related bloodstream infections (CRBSIs) are one of the most prevalent, fatal, and costly complications of hemodialysis with a central venous catheter (CVC). The LOCK IT-100 trial compared the efficacy and safety of a taurolidine/heparin catheter lock solution that combines taurolidine 13.5 mg/ml and heparin (1000 units/ml) versus heparin in preventing CRBSIs in participants receiving hemodialysis *via* CVC.

Methods LOCK IT-100 was a randomized, double-blind, active-control, multicenter, phase 3 study that enrolled adults with kidney failure undergoing maintenance hemodialysis *via* CVC from 70 US sites. Participants were randomized 1:1 to taurolidine/heparin catheter lock solution or heparin control catheter lock solution (1000 units/ml). The primary end point was time to CRBSI as assessed by a blinded Clinical Adjudication Committee. Secondary end points were catheter removal for any reason and loss of catheter patency. On the basis of a prespecified interim analysis, the Data and Safety Monitoring Board recommended terminating the trial early for efficacy with no safety concerns.

Results In the full analysis population (N=795), nine participants in the taurolidine/heparin arm (n=397; 2%) and 32 participants in the heparin arm (n=398; 8%) had a CRBSI. Event rates per 1000 catheter days were 0.13 and 0.46, respectively, with the difference in time to CRBSI being statistically significant, favoring taurolidine/heparin ($P < 0.001$). The hazard ratio was 0.29 (95% confidence interval, 0.14 to 0.62), corresponding to a 71% reduction in risk of CRBSIs with taurolidine/heparin versus heparin. There were no significant differences between study arms in time to catheter removal for any reason or loss of catheter patency. The safety of taurolidine/heparin was comparable with that of heparin, and most treatment-emergent adverse events were mild or moderate.

Conclusions Taurolidine/heparin reduced the risk of developing a CRBSI in study participants receiving hemodialysis *via* CVC compared with heparin with a comparable safety profile.

Clinical Trial registry name and registration number Study Assessing Safety & Effectiveness of a Catheter Lock Solution in Dialysis Patients to Prevent Bloodstream Infection, NCT02651428.

CJASN 18: 1446–1455, 2023. doi: https://doi.org/10.2215/CJN.0000000000000278

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Introduction

Hemodialysis patients are at high risk for bloodstream infections because of the need for frequent vascular access *via* central venous catheter (CVC) and their immunocompromised status.[1] Catheter-related bloodstream infections (CRBSIs) are associated with higher risk of mortality and can lead to complications, such as metastatic infections.[2–4] Although CVCs comprise approximately 19% of hemodialysis vascular accesses, they account for 70% of access-related bloodstream infections.[5] In 2021, approximately 36,000 cases of CRBSIs associated with CVCs occurred in the United States.[6] The highest rates of hemodialysis-associated bloodstream infections occur in Black and Hispanic patients.[7] The average hospitalization cost of CRBSIs with hemodialysis CVCs is ~$17,000–$32,000 per episode and is higher with systemic infections and sepsis.[8] Given the significant morbidity, mortality, and cost associated with CRBSIs in CVC-dependent patients, prevention of CRBSIs is an unmet need in hemodialysis.[9]

Antimicrobial lock solutions can prevent CRBSIs.[10] Taurolidine/heparin is a novel antimicrobial catheter lock solution that combines taurolidine 13.5 mg/ml and heparin (1000 units/ml). Taurolidine is an antibacterial and antifungal agent with a mechanism of action that does not lend itself to resistance.[11,12] Taurolidine/heparin is designed to be instilled and dwell in the arterial and venous lumens of the CVC after each hemodialysis session. It is aspirated before initiation of the next session, without intended systemic administration.[13]

In the United States, heparin is the current standard-of-care catheter lock solution to prevent thrombosis. Heparin, however, does not have any antimicrobial properties. Taurolidine/heparin catheter lock solution is an investigational drug in the United States for CRBSI prevention in patients receiving hemodialysis *via* CVC. We report results from the phase 3 LOCK IT-100 study designed to evaluate the efficacy and safety of taurolidine/heparin catheter lock solution compared with heparin control for the prevention of CRBSIs in participants with kidney failure receiving hemodialysis *via* CVC.

Methods

Study Design and Participants

LOCK IT-100 (ClinicalTrials.gov Identifier: NCT02651428; registration date: January 7, 2016) was a randomized, double-blind, active-control, multicenter, phase 3 study. Participants with kidney failure undergoing hemodialysis using a permanent tunneled cuffed silicone or polyurethane CVC were enrolled from 70 centers in the United States. Eligible participants were aged 18 years or older and underwent hemodialysis ≥2 times per week in an outpatient hemodialysis unit. Catheters were required to be in place for ≥14 days and to have been used successfully to dialyze the participant ≥2 times before enrollment. Exclusion criteria included treatment with antibiotics ≤14 days of enrollment, catheter exit-site infection, thrombolytic treatment (*i.e.*, tissue plasminogen activator) in the patient's current catheter ≤30 days of randomization, systemic immunosuppression (*e.g.*, patients actively on immunosuppressants), or malignancy with life expectancy ≤6 months. Detailed inclusion and exclusion criteria are listed in the Supplemental Methods.

Participants were screened to determine eligibility for enrollment ≤14 days before dosing. On day 1, participants were randomly assigned to taurolidine/heparin or heparin (1000 units/ml) to be instilled after hemodialysis. For subsequent dialysis sessions, taurolidine/heparin or heparin was removed from the hemodialysis catheter before initiation of dialysis and instilled as a fresh lock solution at the end of dialysis. Study visits occurred on dialysis treatment days when standard laboratory data for maintenance dialysis were collected. Every 4 weeks (±5 days), a more extensive visit occurred, including collection of vital signs and laboratory testing. A final safety visit occurred 28 days (+7 days) after removal of the last dose of study drug. Participants remained in the study until they met one of the following criteria: had a CRBSI, completed all assessments through study closure, withdrew from the study (including death), had catheter removed for any reason, or transferred to a nonstudy site. Participants not returning to the study site for follow-up visits and not able to be contacted by the site staff were counted as protocol violations. All participants received standard of care consistent with current practice guidelines for all aspects of hemodialysis. At each hemodialysis center, a nephrologist served as medical director, and daily care was provided by a team of clinical professionals, including nephrologists, registered nurses, and technicians. On suspicion of CRBSI, participants were evaluated by clinical staff of the hemodialysis center and often referred to the emergency department for a more thorough evaluation and treatment. Participants also may have developed symptoms outside a dialysis session and presented directly to an emergency department. CRBSIs were assessed after blood cultures were obtained and confirmed on the basis of medical records from an acute care setting (*e.g.*, hospital or dialysis unit).

The trial was conducted in accordance with the principles of the Declaration of Helsinki and applicable laws and regulations. The protocol and informed consent form were reviewed by a centralized institutional review board. All participants provided written informed consent. The trial had ongoing assessment by an independent Data and Safety Monitoring Board (DSMB) comprising two nephrologists, an infectious disease specialist, and a statistician.

Randomization and Blinding

Participants were randomized 1:1 to either taurolidine/heparin or heparin. Randomization was done centrally *via* an interactive voice/web response system using permuted blocks of size 4 without additional stratification. At randomization, once eligibility was confirmed, the site staff used the interactive system to obtain a randomization number and the first vial of assigned treatment. All participants, investigators, study staff, and dialysis center staff were blinded to treatment assignment. The kit number was assigned and blinded treatment administered per protocol. Only registered nurses were allowed to access CVCs and instill and aspirate the catheter lock solution.

Taurolidine/heparin matched heparin control for volume, color, viscosity, and smell and was packaged in identical containers at an off-site, central facility. The labels remained affixed to the product containers and contained all identifying information except for the identity of the drug. The blind was not broken until the database was locked.

Outcomes

The primary end point was time to CRBSI, which required that the same organism was grown from ≥1 blood culture from a peripheral site or bloodline sample and either the arterial or venous catheter hub (or the venous or arterial dialysis circuit bloodlines if on dialysis)[14] as well as the clinical suspicion of infection. The necessary clinical indication for suspicion of infection included one of the following symptoms: fever (≥37.8°C) or rigors, often with sweating, as documented by a medical professional, or ≥2 of the following symptoms: tachycardia (heart rate >100 beats per minute), tachypnea (>24 breaths per minute), systolic BP <90 mm Hg or a decrease >30 mm Hg, or a change in mental status from baseline. Each potential

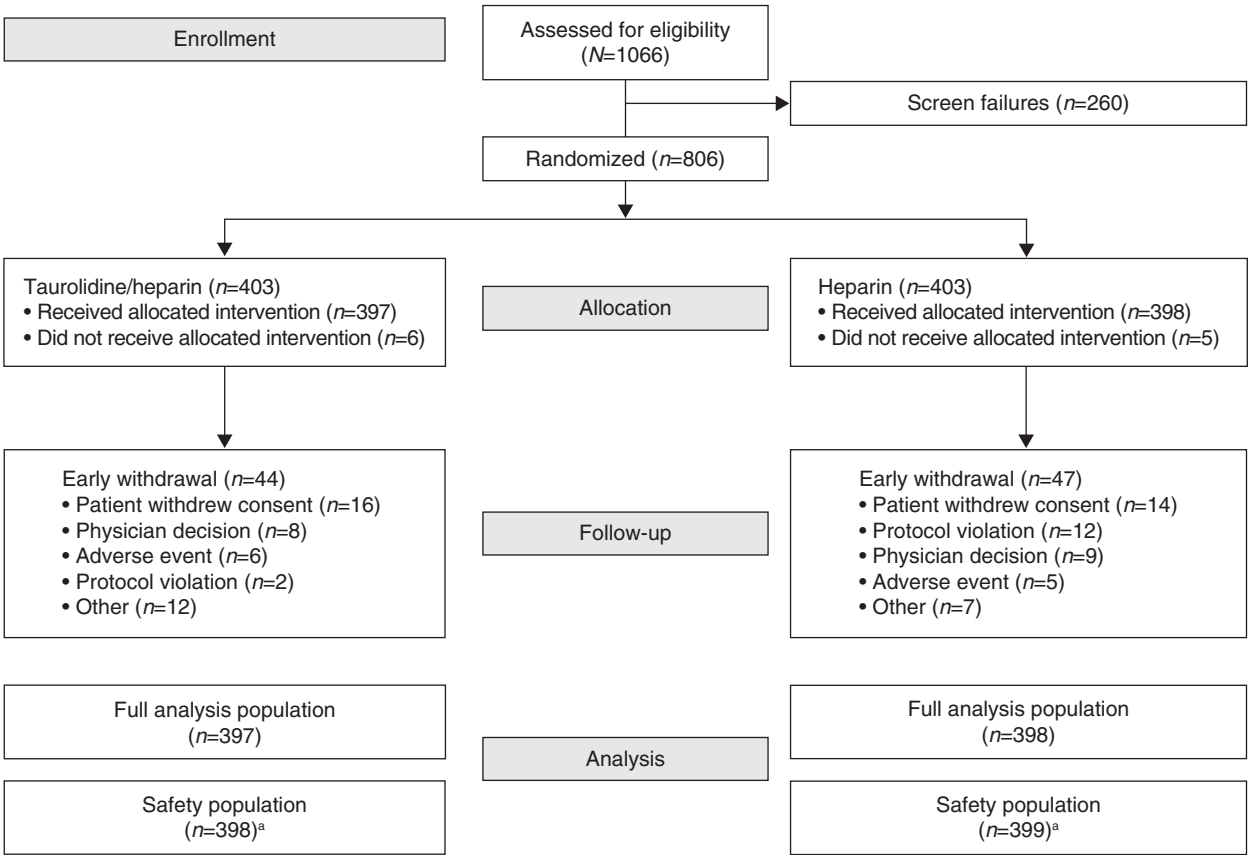

Figure 1. Study flow diagram. [a]Two participants with laboratory values at screening not meeting eligibility criteria were mistakenly dosed without being randomized (one in each study arm) and were subsequently withdrawn. These two participants were included in the safety population but not the full analysis population.

primary end point event was reviewed for ascertainment of CRBSI by a blinded independent Clinical Adjudication Committee. Secondary end points assessed the impact of study drug on catheter functioning and included catheter removal for any reason and loss of catheter patency. Catheter removal because of improvement was defined as the catheter being no longer needed for hemodialysis (*e.g.*, transplant, fistula maturation) or improved kidney function. Catheter removal because of suspected CRBSI was based on the clinician's judgment. Loss of catheter patency was defined as required use of tissue plasminogen activator or removal of catheter because of dysfunction.

The study was originally designed to ascertain CRBSI cases on the basis of pathogen culturing by a centralized laboratory using samples collected from both the patient's peripheral blood and catheter after clinical indications of infection during a dialysis session. Most participants presented with symptoms of infection outside the dialysis center, and the standard of care for collection of blood samples to diagnose CRBSI at an emergency facility or hospital is a single peripheral blood culture. Consequently, the protocol was modified in consultation with the US Food and Drug Administration to define the required information to be collected (including all blood culture results) from medical center records where the patient presented with evidence of infection.[14,15] The information was analyzed by the Clinical Adjudication Committee, which could request additional information to ensure no other sources of infection were present, such as catheter exit-site infections.

Safety parameters included adverse events, clinical laboratory evaluations, vital signs, and physical examination findings. Treatment-emergent adverse events (TEAEs), defined as those that began or worsened on or after administration of the first dose of study drug up to 28 days after the last dose, were coded using *Medical Dictionary for Regulatory Activities* version 21.0. Definitions for serious adverse events are provided in the Supplemental Methods.

Statistical Analyses

This trial was designed to achieve 80% power for comparison of the primary end point between study arms according to the following specifications: testing conducted at a two-sided overall 5% alpha level, taurolidine/heparin associated with a 55% reduction in CRBSI risk relative to control (*i.e.*, risk reduction that might be expected on the basis of previous studies[16,17,18]), and one interim analysis performed at the trial midpoint with adjustment of the alpha level using the method of Pocock. In total, 56 CRBSI events were needed to achieve the desired power, and event rates were monitored over the course of the trial to determine the times of the interim and final statistical

Table 1. Baseline demographic and disease characteristics of participants in the LOCK IT-100 study

Characteristic	Taurolidine/Heparin (n=403)	Heparin (n=403)
Age, mean (SD), yr	61 (14)	61 (14)
Age category, yr, No. (%)		
<65	239 (59)	236 (59)
≥65 to <75	99 (25)	95 (24)
≥75	65 (16)	72 (18)
Female, No. (%)	184 (46)	154 (38)
Race, No. (%)		
American Indian or Alaska Native	3 (1)	2 (<1)
Asian	15 (4)	18 (4)
Black	126 (31)	112 (28)
Native Hawaiian or other Pacific Islander	10 (2)	4 (1)
White	248 (62)	262 (65)
Others	1 (0.2)	5 (1)
Ethnicity, No. (%)		
Not Hispanic or Latino	226 (56)	214 (53)
Hispanic or Latino	177 (44)	189 (47)
BMI, mean (SD), kg/m^2[a]	29.7 (7.9)	29.2 (10.3)
Diabetes, No. (%)	278 (69)	277 (69)
Time since first dialysis, mo[b]		
Mean (SD)	21.2 (37.5)	19.8 (37.0)
Minimum, maximum	0.2, 280.2	0.1, 254.8
Time receiving dialysis, No. (%)		
≤30 d	35 (9)	31 (8)
1–12 mo	237 (59)	246 (61)
>12 mo	131 (33)	126 (31)
Catheter location, No. (%)		
Jugular vein	371 (92)	365 (91)
Subclavian vein	30 (7)	31 (8)
Others[c]	2 (<1)	6 (1)

BMI, body mass index.
[a]Taurolidine/heparin, n=401; heparin, n=402.
[b]Taurolidine/heparin, n=403; heparin, n=402.
[c]The classification of participants as others was due to site staff data entry errors. Catheter location (jugular or subclavian) for these participants was confirmed after data entry and documented in study records.

analyses. It was expected that approximately 900 participants would be randomized.

The primary end point was analyzed in a planned interim analysis on the basis of the first 28 cases of CRBSI (half the required total of 56 events), as adjudicated by the Clinical Adjudication Committee. If statistical significance was obtained for the primary end point at this time, the DSMB would recommend terminating the study early for efficacy. If the futility analysis indicated continuing the study would be futile, the recommendation would be to terminate the study for futility.

The primary end point was analyzed in the interim analysis and at study completion in the full analysis population, which included all randomized participants who received ≥1 dose of study drug. Time to CRBSI was compared between study arms using a log-rank test at an overall two-sided 5% alpha level. The null hypothesis was that there is no difference in CRBSI risk between the two arms. Participants were censored in this analysis at the time of catheter removal for reasons other than CRBSI (*e.g.*, catheter no longer required), patient withdrawal, 3 days after the last dose of study drug administration, or study completion. Because an interim analysis was to be performed, the method of Pocock was used to control the overall alpha level. Therefore, the nominal significance level at the interim and final statistical analyses for the primary end point was 0.0294. A Cox proportional hazards model was used to estimate the hazard ratio (HR; active/control) with 95% confidence interval (CI). CRBSI incidence rate, calculated as the number of participants with CRBSI divided by the aggregate number of catheter days of follow-up, was calculated for each group. Catheter days were counted as the number of days from randomization until the occurrence of either a CRBSI or censoring. CRBSI rates are presented as the event rate per 1000 catheter days with a 95% CI, which was derived assuming the number of catheter days until CRBSI followed an exponential distribution. A prespecified sensitivity analysis of time to CRBSI in the full analysis population was performed in which cases considered to be indeterminate by the Clinical Adjudication Committee were treated as CRBSIs. The primary end point was also assessed in the full analysis population using HRs for prespecified subgroups on the basis of baseline characteristics (age, race, sex, time since first dialysis, and catheter location).

The secondary end points of time until catheter removal for any reason and time to loss of catheter patency were analyzed using similar methods as for the primary analysis. Participants were considered censored as of their final clinical assessment if the event was not observed. Otherwise, event time was the number of catheter days between randomization and event. Secondary end points were

Table 2. Time to catheter-related bloodstream infection (primary outcome, full analysis population)

Outcome Assessment	Taurolidine/Heparin		Heparin
Interim efficacy and futility analyses			
Total No. of participants	327		326
Participants with CRBSI, No. (%)	6 (2)		22 (7)
Total catheter days follow-up[a]	43,954		44,836
CRBSIs per 1000 catheter days (95% CI)	0.14 (0.06 to 0.30)		0.49 (0.32 to 0.75)
HR (95% CI)[b]		0.28 (0.11 to 0.70)	
P value[c]		0.003	
Study completion			
Total No. of participants	397		398
Participants with CRBSI, No. (%)	9 (2)		32 (8)
Total catheter days follow-up[a]	67,593		68,890
CRBSIs per 1000 catheter days (95% CI)	0.13 (0.07 to 0.26)		0.46 (0.33 to 0.66)
HR (95% CI)[b]		0.29 (0.14 to 0.62)	
P value[c]		0.001	

CRBSI, catheter-related bloodstream infection; CI, confidence interval; HR, hazard ratio.
[a]Catheter days were counted as the number of days from randomization up through the occurrence of either a catheter-related bloodstream infection event or censoring.
[b]Cox proportional hazards model.
[c]Log-rank test.

analyzed in the full analysis population using a fixed-sequence testing procedure. The analysis comparing the two groups for catheter loss for any reason was to be formally conducted only if the primary end point analysis yielded a statistically significant result, favoring taurolidine/heparin. The analysis comparing loss of patency was to be formally conducted only if the analysis for catheter loss for any reason also yielded a statistically significant result, favoring taurolidine/heparin. In addition to basic descriptive statistics, rates per 1000 days of follow-up are presented for both end points. *Post hoc* analyses were performed to assess reasons for catheter loss and are summarized by study group.

Safety analyses were conducted on the safety population, which included all participants who received ≥1 dose of study drug. Adverse event data were collected from day

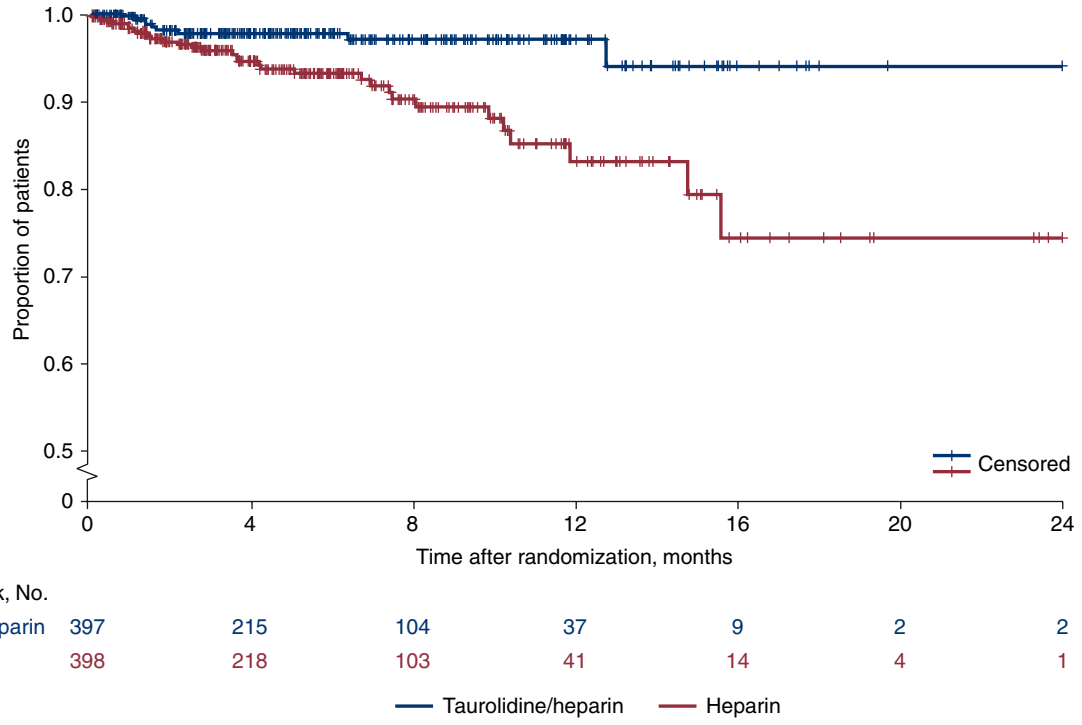

Figure 2. Kaplan–Meier survival curve for time to CRBSI through 24 months (primary outcome, full analysis population). CRBSI, catheter-related bloodstream infection.

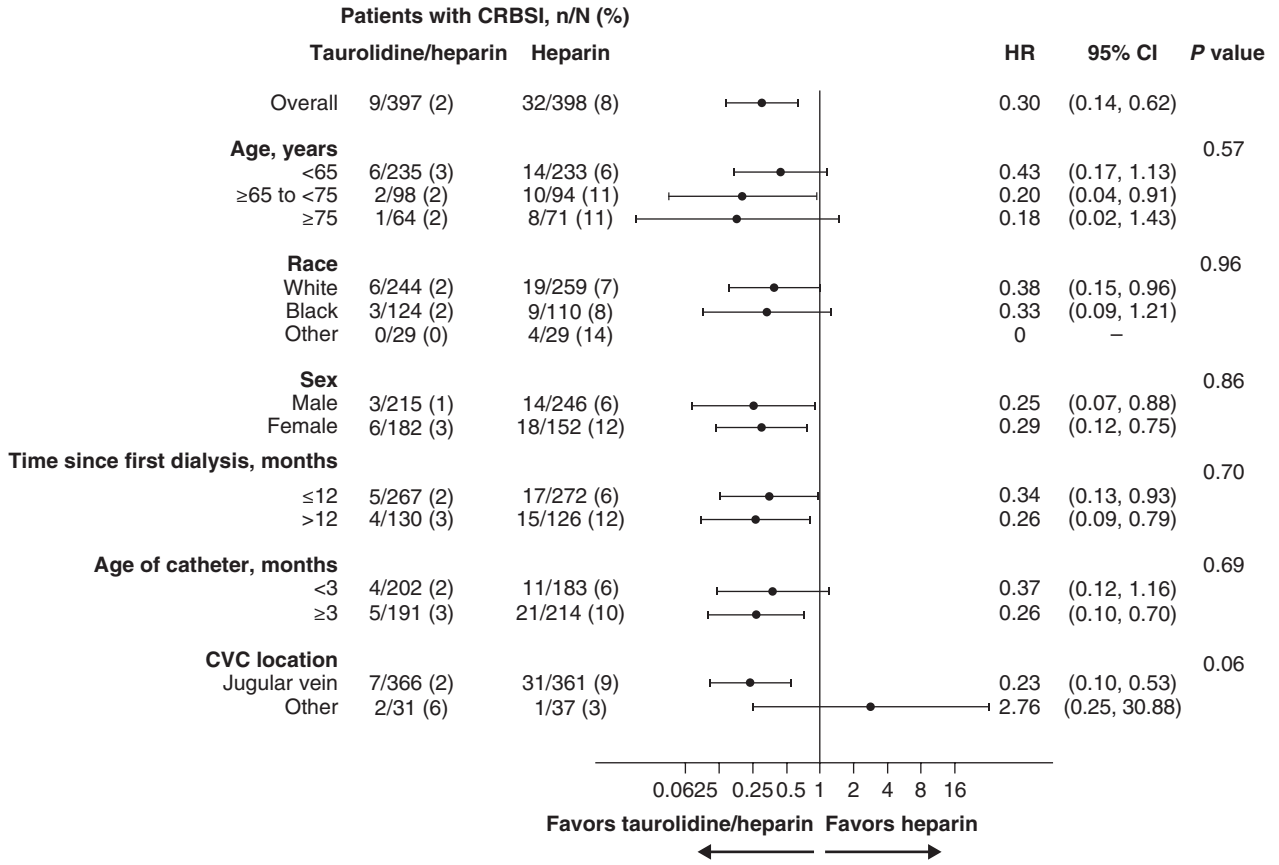

Figure 3. HR (95% CI) of incidence of CRBSI by subgroups (primary outcome, full analysis population). CI, confidence interval; CVC, central venous catheter; HR, hazard ratio.

1 through 28 days after the last removal of study drug. TEAEs were summarized by preferred term and study group, with the number and percentage of participants reporting the event.

Statistical analyses were conducted by an independent statistical group using SAS version 9.4.

Results

Patient Disposition and Baseline Characteristics

Of the 1066 participants screened, 806 were randomized to taurolidine/heparin or heparin (403 participants in each arm; Figure 1). Eleven participants did not receive any doses of study drug and were excluded from the analyses. In the full analysis population, there were 795 participants (taurolidine/heparin arm, $n=397$; heparin arm, $n=398$). In the safety population, there were 797 participants (taurolidine/heparin arm, $n=398$; heparin arm, $n=399$). Two participants with laboratory values at screening not meeting eligibility criteria were mistakenly dosed without being randomized (one in each study arm) and subsequently withdrawn. They are included in the safety population but not the full analysis population. Among randomized participants, 715 (89%) completed the study. The mean length of follow-up in the full analysis population was 200 days (SD, 142 days).

The study population reflected hemodialysis patients in the United States, with 41% aged 65 years and older; 30%, 45%, and 42% self-identifying as Black, Hispanic, and female, respectively; 70% with a body mass index ≥30 kg/m^2; and 69% with diabetes at baseline (Table 1). Most (68%) participants had been receiving dialysis for ≤12 months. All baseline demographic/disease characteristics were balanced between study arms.

Efficacy—Primary Outcome

The primary end point was analyzed as planned at the interim analysis once the first 28 CRBSI cases were adjudicated by the Clinical Adjudication Committee. There were six participants (2%) with CRBSI in the taurolidine/heparin arm versus 22 (7%) in the heparin arm, with event rates per 1000 catheter days of 0.14 and 0.49, respectively (Table 2). The analysis of time to CRBSI yielded a P value of 0.003, favoring taurolidine/heparin. The HR (95% CI) was 0.28 (0.11 to 0.70), corresponding to a 72% reduction in CRBSI risk with taurolidine/heparin versus heparin. This highly statistically significant result, favoring taurolidine/heparin with no safety concerns, resulted in a DSMB recommendation to terminate the study early.

After discussing the DSMB recommendation to terminate the study with the US Food and Drug Administration, additional information was collected per protocol as

Table 3. Time to catheter removal and reasons for removal (secondary outcome, full analysis population)

Outcome Assessment	Taurolidine/Heparin (n=397)	Heparin (n=398)
Participants with catheter removal, No. (%)	236 (59)	225 (57)
Time to catheter removal, median (95% CI), d	197 (171 to 224)	225 (187 to 248)
Total catheter days follow-up[a]	67,912	69,575
Event rate per 1000 catheter days (95% CI)	3.48 (3.06 to 3.95)	3.23 (2.84 to 3.69)
HR (95% CI)[b]	1.08 (0.90 to 1.29)	
P value[c]	0.42	
Catheter removal because of improvement[d]		
Participants with catheter removal because of improvement, No. (%)	162 (41)	132 (33)
No longer needed for hemodialysis, No. (%)	162 (41)	131 (33)
Improved kidney function	0	1 (0.3)
Total catheter days follow-up	67,780	69,465
Event rate per 1000 catheter days (95% CI)	2.39 (2.05 to 2.79)	1.90 (1.60 to 2.25)
Catheter removal because of CRBSI or catheter malfunction		
Participants with catheter removal because of CRBSI, catheter malfunction, or other reasons, No. (%)	74 (19)	93 (23)
Catheter malfunction/dysfunction, No. (%)	62 (16)	57 (14)
Loss of patency	28 (7)	26 (7)
Others	34 (9)	31 (8)
CRBSI	8 (2)	29 (7)
Others	4 (1)	7 (2)
Total catheter days follow-up	67,708	69,318
Event rate per 1000 catheter days (95% CI)	1.09 (0.87 to 1.37)	1.34 (1.09 to 1.64)

CI, confidence interval; HR, hazard ratio; CRBSI, catheter-related bloodstream infection.
[a]Catheter days were counted as the number of days from randomization up through the occurrence of catheter removal (for any reason) or censoring.
[b]Cox proportional hazards model.
[c]Log-rank test.
[d]Catheter was no longer needed for hemodialysis (*i.e.*, transplant, fistula maturation) or because of improved kidney function.

orderly termination of study participants proceeded. At study completion, nine participants (2%) had a CRBSI in the taurolidine/heparin arm versus 32 (8%) in the heparin arm, with a clinically significant lower event rate per 1000 catheter days for taurolidine/heparin (0.13 versus 0.46, respectively; Table 2). Time to CRBSI was highly statistically significantly different between arms, favoring taurolidine/heparin ($P < 0.001$). The Kaplan–Meier curve for time to CRBSI through 24 months is shown in Figure 2. The HR (95% CI) was 0.29 (0.14 to 0.62), corresponding to a 71% reduction in CRBSI risk with taurolidine/heparin versus heparin. The results of the sensitivity analysis, considering indeterminate cases as positive for CRBSI, were consistent with those of the primary analyses.

In prospectively defined subgroup analyses of the primary end point, the HR estimates were, with one minor exception (*i.e.*, the small subgroup of participants with catheter locations other than the jugular vein), consistently <0.5, corresponding to a >50% reduction in risk, favoring taurolidine/heparin (Figure 3).

Secondary Outcomes

There was no statistically significant difference between arms at study completion in time to catheter removal for any reason, a secondary end point of the trial (Table 3). The median time to catheter removal for any reason was 197 days for taurolidine/heparin and 225 days for heparin, with an HR (95% CI) of 1.08 (0.90 to 1.29). *Post hoc* analyses performed to assess and describe incidences and reasons for catheter removal are described in Table 3, Supplemental Results, and Supplemental Table 1. The analysis of loss of catheter patency is described in the Supplemental Results and Supplemental Table 2.

Safety

Overall, 314 participants (79%) in the taurolidine/heparin arm and 315 (79%) in the heparin arm experienced a TEAE (Table 4). Most TEAEs were mild to moderate in intensity, with no serious TEAEs with a probable or definite relationship to the study drug as determined by the investigator. There were no reported TEAEs associated with the infrequent inadvertent flushing of taurolidine/heparin through the catheter into the body. Early withdrawals because of TEAEs were infrequent and comparable between arms. The taurolidine/heparin and heparin arms saw a similar death rate (5%). The most common cause of death was cardiac disorders (five participants in each arm). Information on specific TEAEs is provided in the Supplemental Results.

Discussion

In LOCK IT-100, taurolidine/heparin significantly reduced CRBSIs in participants receiving hemodialysis *via* CVC for the treatment of kidney failure compared with heparin, the current standard of care. There were no significant differences in rates of catheter removals for any reason or loss of catheter patency between study arms. The safety profile for taurolidine/heparin was comparable with that of heparin.

LOCK IT-100 is the largest randomized, double-blind, active-comparator trial conducted to date in US participants

Table 4. Summary of treatment-emergent adverse events (safety population)

Participants with Events, No. (%)	Taurolidine/Heparin (n=398)	Heparin (n=399)
Any TEAE	314 (79)	315 (79)
Mild	91 (23)	80 (20)
Moderate	112 (28)	102 (26)
Severe	89 (22)	112 (28)
Life-threatening	22 (6)	21 (5)
Serious TEAE	159 (40)	167 (42)
Drug-related TEAE	17 (4)	13 (3)
TEAE leading to early withdrawal from the study	4 (1)	5 (1)
TEAE (cardiac) with an outcome of death	5 (1)	5 (1)
Serious TEAE related to study drug[a]	1 (0.3)	0
Serious TEAEs occurring in ≥2% of participants in either study arm		
Pneumonia	12 (3)	21 (5)
Fluid overload	14 (4)	12 (3)
Sepsis	9 (2)	14 (4)
Acute myocardial infarction	5 (1)	13 (3)
Cardiac failure, congestive	12 (3)	7 (2)
Hyperkalemia	10 (3)	8 (2)
Hypertension	4 (1)	10 (3)
Respiratory failure	7 (2)	9 (2)
Device-related infection	6 (2)	8 (2)

TEAE, treatment-emergent adverse event.
[a]Includes one event of device malfunction that was considered possibly related to the study drug by the investigator. There were no serious treatment-emergent adverse events with a probable or definite relationship to the study drug.

receiving hemodialysis *via* CVC. It was conducted at 70 investigative centers with 150 outpatient dialysis units. Centers included large dialysis organizations, independent centers, and the US Veterans Affairs system.

The finding in this study of a 71% reduction in CRBSIs with the use of taurolidine/heparin is consistent with the findings of two earlier studies in hemodialysis patients.[16,17] Solomon *et al.* found a 59% reduction with the use of taurolidine/heparin in all bloodstream infections (including those not catheter related), and Murray and colleagues reported a 56% reduction in all *Staphylococcus* infections. The results of this study are also consistent with a randomized controlled trial in 106 participants receiving hemodialysis *via* CVC, which reported a CRBSI rate of 0.67 per 1000 catheter days with a taurolidine-based catheter lock solution versus 2.7 per 1000 catheter days with a citrate solution.[19] In this study, rates of total catheter dysfunctions and catheter removal because of infectious and mechanical complications were significantly lower in the taurolidine group. Similarly, a meta-analysis of the efficacy of taurolidine lock solutions in reducing CRBSIs in children reported a 77% reduced risk of CRBSI with taurolidine versus control ($P < 0.00001$).[20]

The results of LOCK IT-100 clearly document a substantial reduction in CRBSIs in CVCs used for hemodialysis. Early termination of the trial by the DSMB speaks to the magnitude of this effect, which will likely result in a significant reduction in morbidity and mortality, as well as better utilization of scarce health care resources. A reduction in CRBSIs may result in an improved quality of life in this vulnerable population by reducing hospitalizations with significant clinical and public policy impacts. The availability of taurolidine/heparin will facilitate a precision medicine approach to vascular access care by benefiting patients who have no choice besides a dialysis CVC because they have run out of possible sites for arteriovenous access. The 2019 Kidney Disease Outcomes Quality Initiative guidance on vascular access emphasizes a new paradigm of getting the right access in the right patient at the right time.[21] Given the continuing need for some patients to dialyze *via* CVC, a safe and effective antimicrobial catheter lock solution will play a very important role in reducing CRBSIs in this patient population.

Reducing CRBSIs in hemodialysis patients will also synergize with new global payment plans. The new Comprehensive Kidney Care Contracting payment plans that are part of the Advancing American Kidney Health Executive Order emphasize a reduction in hospital admissions and readmissions.[22] Reducing CRBSIs in hemodialysis patients will likely increase the efficiency of care and reduce the number and duration of hospitalizations and overall costs.

In conclusion, taurolidine/heparin, a novel antimicrobial catheter lock solution, significantly reduces CRBSI risk in patients receiving hemodialysis *via* CVC versus the standard-of-care heparin without any safety concerns. These findings support the use of taurolidine/heparin in hemodialysis patients to reduce risk of CSRBIs, which are associated with very significant clinical, economic, and quality of life burdens in this vulnerable patient population.

Disclosures

A.K. Agarwal reports employment with VA Central California Health Care System; consultancy for Akebia; honoraria from Amgen; advisory or leadership roles for ASDIN, *Clinical Nephrology*, *Frontiers in Nephrology*, *International Journal of Nephrology*, ISN, *Journal of Vascular Access*, KSAP, NKF, and *The Open Urology & Nephrology Journal* (all unpaid); advisor role to AstraZeneca and Otsuka; research support from Akebia

Pharmaceuticals; and other interests or relationships with ASDIN, ASN, ISN, and NKF. E. Hurlburt reports employment with CorMedix, Inc. P. Mounts reports employment with, ownership interest in, and advisory or leadership role for CorMedix Inc. A. Pfaffle reports employment with, ownership interest in, and advisory or leadership roles for CorMedix Inc. A. Pfaffle has served as the Chief Scientific Officer and Head of Patient Advocacy and Special Projects at CorMedix. E.C. Poggio is the founder and owner of Biostatistical Consulting Inc. (BCI), which provided statistical design and analysis services to CorMedix Inc. BCI provides biostatistical consulting to numerous pharmaceutical, biotech, and medical device companies for which it is paid. E.C. Poggio reports ownership interest in AstraZeneca, Acurx, and Biostatistical Consulting Inc. E.C. Poggio's wife reports employment with AstraZeneca. P. Roy-Chaudhury reports employment with VAMC Salisbury, NC; consultancy for Akebia, Alexion (AstraZeneca Rare Diseases), AstraZeneca, Bayer, Becton Dickinson, CorMedix, Humacyte, Medtronic, Target RWE, and WL Gore; ownership interest as Chief Scientific Officer and Founder of Inovasc LLC; NIH Small Business Grants as MPI or site PI with Adgero, Cylerus, Eko, and Inovasc; honoraria from Akebia, Alexion (AstraZeneca Rare Diseases), AstraZeneca, Bayer, Becton Dickinson, Cormedix, Humacyte, Medtronic, N9, and WL Gore; research funding from Bayer; and advisory or leadership roles for Akebia, Alexion (AstraZeneca Rare Diseases), ASN, AstraZeneca, Bayer, Becton Dickinson, BioMed Innovations, Cormedix, Editorial Board of *Journal of Vascular Access*, Humacyte, Medtronic, N9, Vascular Access Society of the Americas, and WL Gore.

Funding

This study was sponsored by CorMedix Inc.

Acknowledgments

The authors gratefully acknowledge the participating patients; their family members and caregivers; the study center staff members, nursing teams, and medical personnel who cared for the participants; the site primary investigators, the sponsor staff involved in data collection and analyses; and the members of the Data and Safety Monitoring Board and Clinical Adjudication Committee. Staff and consultants to CorMedix Inc., were invaluable to completing LOCK IT-100. Medical writing and editorial support were provided by Kim Fuller, PhD, of Lumanity Communications Inc., and were funded by CorMedix Inc. The results from this study were previously presented in part at the National Kidney Foundation Spring Clinical Meeting 2019; May 8–12, 2019; Boston, Massachusetts. This study is dedicated to the memories of CorMedix Inc. colleagues Sue Willis and Ken Massey who passed away after contributing to the development of this novel antimicrobial catheter lock solution.

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Data Sharing Statement

Anonymized data have been deposited with Zenodo.

Supplemental Material

This article contains the following supplemental material online at http://links.lww.com/CJN/B805.

Supplemental Methods.

Supplemental Results.

Supplemental Table 1. Catheter removal because of other reasons, besides CRBSI or catheter malfunction (full analysis population).

Supplemental Table 2. Loss of catheter patency (full analysis population).

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Received: February 2, 2023 **Accepted:** August 25, 2023
Published Online Ahead of Print: September 6, 2023