Effectiveness and Cost of Weekly Recombinant Tissue Plasminogen Activator Hemodialysis Catheter Locking Solution

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Abstract

Background and objectives Evidence to guide hemodialysis catheter locking solutions is limited. We aimed to assess effectiveness and cost of recombinant tissue plasminogen activator (rt-PA) once per week as a locking solution, compared with thrice weekly citrate or heparin, in patients at high risk of complications.

Design, setting, participants, & measurements We used a prospective design and pre-post comparison in three sites across Canada. Pre-post comparisons were conducted using multilevel mixed effects regression models accounting for cluster with site and potential enrollment of patients more than once. In the pre period, catheter malfunction was managed as per site-specific standard of care. The intervention in the post period was once weekly rt-PA as a locking solution (with citrate or heparin used for other sessions). The primary outcome was rate of rt-PA use for treatment of catheter malfunction. Secondary outcomes included rates of bacteremia, management of catheter malfunction, and cost.

Results There were 374 patients (mean age 68 years; 52% men) corresponding to 506 enrollments. Mean length of enrollment was 200 days (SD 119) in the pre period and 187 days (SD 101) in the post period. There was a significant decline in rate of rt-PA use for treatment of catheter malfunction in the post compared with pre period (adjusted incidence rate ratio, 0.39; 95% confidence interval, 0.30 to 0.52); however, there was no difference in the rate of bacteremia, or catheter stripping or removal/replacement. The increase in mean total health care cost in the post period was CAD$962 per enrollment, largely related to costs of rt-PA as a locking solution.

Conclusions Once weekly rt-PA as a catheter locking solution was associated with a reduction in rt-PA use for treatment of catheter malfunction. Our results showing a reduction in rescue rt-PA use are consistent with a prior randomized trial, although we did not observe a reduction in bacteremia or catheter stripping/removal and did observe an increased incremental cost of this strategy primarily accounted for by the cost of the rt-PA.

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Introduction

Central venous catheters are used by >80% of patients initiating hemodialysis in North America (1–3), with complications including thrombosis and infection (4–7). The median time to a noninfectious complication is 1.8 months for patients with a catheter (6). The majority of noninfectious complications are due to thrombosis resulting in catheter malfunction (8,9). Catheter-related infection is also associated with adverse health outcomes and high health care costs (10,11).

Evidence to guide use of catheter locking solutions is limited. A systematic review of 27 randomized trials (RCTs) (12) reported that, compared with usual care (typically heparin), there was no reduction in catheter malfunction for a variety of interventions, including systemic agents (aspirin; six studies), low- or no-dose heparin (two studies), or alternative locking solutions (citrate, recombinant tissue plasminogen activator [rt-PA],

antibiotic, low-molecular-weight heparin, and ethanol; 19 studies). Of the individual alternative agents, rt-PA, when compared with heparin, was the only locking solution to reduce catheter malfunction, on the basis of a single study. There was, however, a significant reduction in catheter-related bacteremia for alternative anticoagulant locking solutions, including citrate (12 studies), antibiotic (one study), and rt-PA (one study).

In an RCT comparing heparin to once weekly rt-PA as a catheter locking solution (13), we noted a two-fold higher risk of malfunction among patients treated with heparin only, whereas the risk of bacteremia was three-fold higher. Although these results suggest that rt-PA once weekly may reduce the incidence of catheter malfunction and bacteremia, generalizability of results is limited due to comparison with heparin (citrate is now commonly used [12]), and inclusion of unselected incident hemodialysis patients, regardless of their risk for complications.

Given these concerns, and cost of rt-PA, we undertook a pragmatic, multicenter, prospective study to assess the effectiveness and cost of rt-PA once per week as a locking solution, as compared with citrate or heparin, for prevention of catheter-related malfunction and bacteremia in patients receiving hemodialysis at high risk of catheter complications.

Materials and Methods

We used a prospective design and pre-post comparison in three sites across Canada. Pre-post comparisons were conducted using multilevel mixed effects regression models accounting for cluster with site and potential enrollment of patients more than once.

Eligible Patients and Time Periods

Eligible patients included adults (18 years of age and older) undergoing chronic hemodialysis with a tunneled catheter at outpatient hemodialysis clinics at three sites across Canada: Vancouver, British Columbia; Calgary, Alberta; and Halifax, Nova Scotia. Patients with a newly inserted catheter (incident), or an existing catheter (prevalent), were considered. Patients with an incident catheter were eligible 2 weeks after catheter insertion, because catheter malfunction within 2 weeks may be more likely due to a mechanical cause rather than thrombosis.

We enrolled patients at high risk of catheter malfunction or bacteremia, defined as at least one of the following: catheter reversal (for any portion of the hemodialysis session) at least three times in the prior six sessions, use of rt-PA twice (on two separate occasions) in the prior six sessions for treatment of malfunction, two episodes of catheter-related bacteremia in the prior 12 months, or limited access options (medically or by patient choice) as deemed by the study site, with potential for benefit from a prophylactic locking solution (14). Patients were ineligible if they were at high risk of bleeding, as previously defined (13).

Two separate time periods were studied. The pre period consisted of at least 6 months before the implementation of the weekly rt-PA prophylaxis protocol, and the post period included at least 6 months post introduction of the protocol. Patients were identified using a standard protocol and followed prospectively. A study coordinator at each site was notified of eligible patients by hemodialysis unit staff, and followed patients for study outcomes throughout both periods. The process of patient identification and follow-up was identical in both periods; in the post period eligible patients were initiated on the once weekly rt-PA catheter locking protocol. Patients who had been enrolled in the pre period could also be re-enrolled in the post period if they once again met the eligibility criteria; a new enrollment corresponded either to a catheter replacement, or a patient who re-enrolled in the post period after completing the pre period without a catheter removal.

Intervention–rt-PA Prophylaxis Protocol

The rt-PA locking protocol locked the catheter lumen with rt-PA at a dose of 1.0 mg per lumen, once per week. To ensure that the rt-PA was administered to the catheter tip, the site of thrombus formation, it was instilled down each lumen first, followed by a volume of saline to fill the remaining luminal volume. On the other days, the standard site-specific catheter locking solution was administered postdialysis.

Outcomes

The primary outcome was rate of rt-PA use for treatment of catheter malfunction (rt-PA use as a prophylactic locking solution in the post period was not included in the calculations of these rates). All sites used rt-PA for treatment of catheter malfunction.

Secondary outcomes included: catheter-related bacteremia, defined according to published criteria (15), with both "definite" and "probable" infections included in the outcome (Supplemental Appendix 1); interventions for catheter malfunction (catheter stripping or catheter removal/replacement); bleeding events; vascular access–related hospitalizations; and health care costs. The following categories of health care costs were included (Supplemental Appendix 2): catheter locking solutions (heparin [CAD$5.60 per catheter], 4% sodium citrate [CAD$1.80 per catheter], and rt-PA [CAD$64 per catheter, administered once weekly]); the cost of managing catheter malfunction (including the cost of rescue rt-PA [CAD$32 per ml], the cost of catheter stripping, and/or the cost of catheter replacement [estimated at CAD$1407]); the cost of managing catheter-related bacteremia as an outpatient (CAD$487) (16); and the cost of patients admitted to hospital for this indication (average of CAD$11,995 per admission). Resource use and valuation were based directly on this cohort except for cost of hospitalization where, because of small numbers of admitted patients and some admitted outside of Alberta, we based the cost of hospitalization on microcosting data available from a past study which measured the cost of hospitalization for catheter-related bacteremia (16).

Data Analysis

For the primary outcome, rate of rt-PA use, the numerator consisted of the number of hemodialysis sessions a patient was administered rt-PA for catheter malfunction, and the denominator was the time period at risk (catheter days). For the secondary outcome of rate of bacteremia, the numerator consisted of the number of definite or probable cases of bacteremia, whereas the denominator was catheter days. Patients may have experienced more than one episode of rt-PA use, or bacteremia event, during each period. For both outcomes, pre-post comparisons were conducted using multilevel mixed effects regression models of the Poisson family that included the time period (pre-versus postintroduction of the rt-PA protocol) as the exposure and the duration of enrollment as an offset, and adjusting for other covariates of interest. We used three levels, nesting enrollment within patient, and patient within site, and treated patient and site as random effects. We corrected for over-dispersion as necessary by using negative binomial models, which added a dispersion parameter to the Poisson model. No patients were lost to follow-up.

For the secondary outcome of interventions for catheter malfunction, we created a composite outcome of catheter stripping or catheter removal and replacement for malfunction, whichever occurred first. We conducted pre-post

comparisons using Poisson regression as described above, adjusting for relevant covariates.

For the secondary outcome of cost, given the expected non-Gaussian distribution of costs, we used established methods to enable comparisons of mean costs. We used nonparametric bootstrap estimates to derive SDs and 95% confidence intervals (95% CIs) and mean cost differences between the treatment arms (17,18), as we have done previously (16). Using 1000 bias-corrected bootstrap replications, and on the basis of sampling with replacement from the original data, we estimated the distribution of a sampling statistic to derive 95% CIs (19). In sensitivity analyses, we used generalized linear models to compare total costs across groups (20), using a γ distribution and log-link function (because the performance of this model was best). We repeated our costing analysis using a lower rt-PA cost to determine a break-even point where an rt-PA strategy would not be associated with an incremental cost; or whether a plausible increase in hospitalization costs might lead to similar costs across the two strategies.

Statistical analysis was conducted using Stata 14.2. There were no missing data. Ethics approval was obtained from the Universities of Calgary and British Columbia and the Nova Scotia Research Health Authority. Because this was a quality assurance project with the primary purpose to evaluate the effectiveness of rt-PA at a program level, waiver of individual patient consent was granted.

Results

Across the three sites there were 374 patients and 506 enrollments. Of the 374 patients, 159 (43%) were only in the pre period, 111 (30%) were only in the post period, and 104 (28%) were in both. The majority of patients (256; 68%) had a single enrollment, and of the 118 patients who were enrolled more than once, 108 (29%) were enrolled twice and ten (3%) were enrolled more than twice. Of the 104 patients who participated in both the pre and post periods, 91 completed the pre period and began the post period with the same catheter, whereas 13 terminated their pre participation due to catheter replacement, and began the post period with a new catheter. Of the 506 enrollments, 113 were terminated for catheter removal, 47 died, and 43 left the study for another reason (*e.g.*, conversion to arteriovenous fistula, transplant, moved). The remaining 303 enrollments completed follow-up to end of the pre or post period. The mean length of an enrollment was 200 days (SD 119) in the pre period and 187 days (SD 101) in the post period.

Table 1 presents patient-level baseline characteristics, whereas Table 2 shows additional baseline characteristics defined at the point of enrollment, stratified by time period. The mean age of patients was 68 years, with a mean of 2.4 comorbidities. The most common catheter locking solution was 4% sodium citrate (96%), and most common reason for enrollment was catheter line reversal (76% of enrollments).

Primary Outcome—Rate of rt-PA Use for Treatment of Catheter Malfunction

For the primary outcome, total enrollment was 158.9 person-years in the pre period, and 110.7 person-years in the post period (Figure 1, Table 3). The dose of rt-PA used

Table 1. Overall patient-level baseline characteristics for 374 patients enrolled

Characteristic	$n=374^{a}$
Mean age at first enrollment (SD), yr	68 (15)
Men	52
Primary cause	
Diabetes	40
Hypertension	21
Ischemic kidney vascular disease	9
GN	7
Polycystic kidney disease	4
Other	19
Comorbidities	
Hypertension	89
Diabetes	58
Coronary artery disease	32
Congestive heart failure	24
Cancer	18
Stroke	17
Deep venous thrombosis/pulmonary embolism	6
Mean number of comorbidities	2.43

[a]% unless otherwise indicated.

for treatment ranged from 2 to 4 mg per treatment, depending on the method of administration. For the interdialytic locking as a treatment method, the dose was 1 mg per lumen at all sites. Overall, the rate of rt-PA use for treatment of catheter malfunction declined from 18.4 days per 1000 catheter days in the pre period to 10.1 days per 1000 catheter days in the post period. The unadjusted incidence rate ratio for rt-PA use in the post versus pre period was 0.33 (95% CI, 0.24 to 0.44) and the adjusted incidence rate ratio was 0.39 (95% CI, 0.30 to 0.52), indicating a statistically significant decrease in the rate of rt-PA use for treatment of catheter malfunction from pre to post period. Duration on dialysis was retained in the final model as a potential confounder; there was no evidence of confounding by length of time using the current catheter. When considering total rt-PA use (for both treatment of malfunction and prophylactic as a locking solution), the rate of use was almost five-fold higher in the post period at 325.0 doses (milligrams) per 1000 catheter days, compared with 67.3 doses in the pre period.

Secondary Outcomes

Overall, 23 patients experienced 26 bacteremia episodes, with 13 (50%) episodes resulting in catheter removal. Sixteen episodes occurred in the pre period (0.28 per 1000 catheter days) and ten in the post period (0.25 per 1000 catheter days). The decline in rate of bacteremia was nonsignificant, with an unadjusted incidence rate ratio of 0.92 (95% CI, 0.41 to 2.11) and an adjusted incidence rate ratio of 0.86 (95% CI, 0.38 to 1.93) (Figure 1).

For the secondary composite outcome, there were 97 occurrences of catheter stripping or removal (81 cases of catheter removal due to malfunction; eight cases where catheter stripping was followed on the same day by catheter removal; and eight cases where catheter stripping occurred either without a subsequent catheter removal, or where the removal was at least 1 day later). Overall, 7% of rt-PA treatments (97 of 1475) were followed by catheter stripping

Table 2. Enrollment-level baseline characteristics, by pre versus post period, for 290 enrollments in the pre period and 216 enrollments in the post period

Characteristic[a]	Pre (n=290)	Post (n=216)	Overall (n=506)
Type of catheter			
HemoStar (Bard)	71	68	70
Palindrome (Covidien)	26	31	28
Other	3	1	2
Catheter locking solution			
4% sodium citrate	96	96	96
Heparin 1:1000	2	3	3
Heparin 1:5000	2	1	2
First dialysis catheter ever	35	33	34
Number of previous catheters (including current catheter), median (IQR)	2 (1, 4)	2 (1, 4)	2 (1, 4)
Time on dialysis at enrollment			
Median (IQR), yr	1.8 (0.6, 4.2)	2.5 (1.1, 5.4)	2.0 (0.8, 5.0)
Up to 1 yr	35.5	23.6	30.4
>1–3 yr	29.3	29.2	29.2
>3 yr	35.2	47.2	40.3
Time on current catheter at enrollment			
Median (IQR), yr	0.5 (0.2, 1.3)	0.9 (0.3, 1.7)	0.6 (0.2, 1.5)
<90 d	32	19	27
90 d to 1 yr	34	38	36
>1 yr	34	43	38
Medication use			
Acetylsalicylic acid	48	41	45
Clopidogrel	10	9	10
Warfarin	10	6	9
Plavix	1	1	1
Any of above	60	48	55
Lab measurements at baseline			
Albumin (g/dl), median (IQR)	3.3 (3.0, 3.6)	3.3 (3.0, 3.6)	3.3 (3.0, 3.6)
Hemoglobin (g/dl), median (IQR)	10.7 (10.0, 11.6)	11.0 (10.1, 11.9)	10.8 (10.0, 11.7)
Inclusion criteria (multiple responses possible)			
Catheter line reversal three out of last six sessions	72	81	76
Use of rt-PA two out of last six sessions	21	7	15
Two episodes of catheter bacteremia in last 12 mo	2	3	3
Limited access options	24	22	23

IQR, interquartile range.
[a]% unless otherwise indicated. Percentages do not necessarily sum to 100 due to rounding.

or removal. A total of 63 events occurred in the pre period (1.10 per 1000 catheter days), whereas 34 occurred in the post period (0.84 per 1000 catheter days). The decline in rate of catheter stripping/removal was nonsignificant, with an unadjusted incidence rate ratio of 0.71 (95% CI, 0.41 to 1.21) and an adjusted incidence rate ratio of 0.86 (95% CI, 0.53 to 1.40) (Figure 1).

Overall, there were 13 major bleeding events; six in the pre and seven in the post period. After taking time at risk into account, there was no significant difference in the rate of bleeding events (incidence rate ratio, 1.67; 95% CI, 0.57 to 4.96). There were 134 hospitalizations overall; however, only eight of these were catheter related (six in the pre and two in the post period). None of the hospitalizations ended in death.

Health Care Costs. The unadjusted mean total health care cost per enrollment in the post compared with the pre period was CAD$2496 (95% CI, 2240 to 2750) and CAD$1543 (95% CI, 981 to 2106), respectively. After bootstrapping, the mean unadjusted difference was CAD$962 (95% CI, 354 to 1571; P=0.002) (Table 4). The cost of the weekly prophylactic rt-PA catheter locking solution in the post period accounted for the largest proportion of the overall cost. To assess the robustness of the bootstrapping method for comparing costs, we also used generalized linear regression and a γ distribution with a log link to compare

costs, noting a similar difference in adjusted costs between the post and pre period (CAD$985; 95% CI, 254 to 1717; P<0.01). To assess how much lower the price of rt-PA would need to be to ensure an rt-PA strategy that was not associated with an incremental cost, we reran the analysis using lower costs, noting that the cost of rt-PA would need to be priced at CAD$12/ml (actual current cost of CAD$32/ml) to break even.

Discussion

In this pragmatic, prospective, multicenter study with a pre-post comparison, we found that, compared with a thrice weekly standard locking solution (primarily 4% sodium citrate), use of rt-PA as a catheter locking solution once weekly reduced the rate of rt-PA use for treatment of catheter malfunction among patients undergoing hemodialysis at high risk of catheter complications. However, net rt-PA use overall was five-fold higher in the post period compared with the pre period, and accounted for most of the difference (CAD$962 per enrollment) in mean total health care costs between the two periods. Once weekly rt-PA use was not associated with reductions in the likelihood of bacteremia or catheter stripping/removal for malfunction, although the number of events was small.
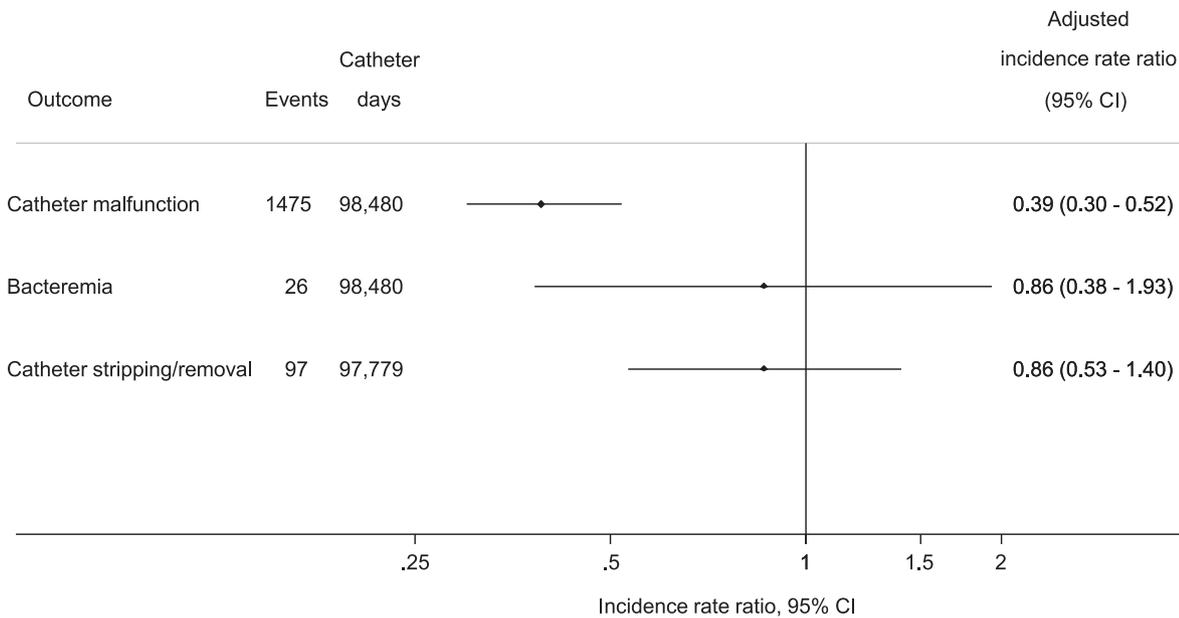
Figure 1. | **Forest plot of adjusted incidence rate ratio for the primary outcome of rt-PA use for catheter malfunction, and secondary outcomes of bacteremia and catheter stripping/removal.** The rate of rt-PA use for catheter malfunction outcome was adjusted for age, sex, inclusion criteria, prior rate of catheter replacement, duration on dialysis, and history of stroke or deep venous thrombosis/pulmonary thrombosis. The bacteremia outcome was adjusted for sex and first catheter ever. The catheter stripping/removal outcome was adjusted for the number of catheter replacements per year before enrollment, inclusion criteria, and age. 95% CI, 95% confidence interval; rt-PA, recombinant tissue plasminogen activator.

Noninfectious complications of hemodialysis catheters (primarily thrombosis) are common, with rates of 21.9 events per 1000 catheter days within the first month of catheter use, and remaining >2.1 events per 1000 days even after the first year (6). These episodes lead to shortened dialysis treatments and less adequate dialysis with increased morbidity (21), as well as the overall negative effect

Table 3. Primary outcome of rate of rt-PA use for treatment of catheter malfunction

Variable	Pre Period	Post Period
Total number of dialysis sessions with use of rt-PA for treatment of catheter malfunction	1068	407
Total catheter days	58,050	40,430
rt-PA use days per 1000 catheter days	18.40	10.07
Unadjusted incidence rate ratio for post versus pre rate of outcome (95% confidence interval)	0.33 (0.24 to 0.44)[a]	
Adjusted incidence rate ratio for post versus pre rate of outcome (95% confidence interval)	0.39 (0.30 to 0.52)[a,b]	

rt-PA, recombinant tissue plasminogen activator.
[a] From a three-level mixed effects negative binomial regression model, with enrollment nested within person and person nested within site. Person and site were treated as random effects.
[b] Adjusted for age, sex, inclusion criteria, prior rate of catheter replacement, duration on dialysis, stroke, and history of deep venous thrombosis/pulmonary embolism.

on patient satisfaction and quality of life (22). However, evidence to guide the use of locking solutions for primary prevention of malfunction is limited (12). Consistent with our prior RCT of once weekly rt-PA use as a catheter locking solution (13), in this study of rt-PA in a real world clinical setting of patients at high risk of catheter complications, we found a significant reduction in catheter malfunction as defined by the rate of rt-PA use for treatment, which is commonly used for treatment of catheter malfunction. On the basis of patients receiving incident dialysis in the United States, Xue *et al.* (7) reported that nearly one in three (32.5%) who initiated dialysis with a catheter required rt-PA for malfunction by a median of 41 days postinsertion. Over half required more than one dose of rt-PA, and approximately one in six (17.9%) eventually had the catheter replaced due to malfunction.

However, unlike our prior RCT (13), we did not find a reduction in rates of bacteremia when rt-PA was used once weekly as a catheter locking solution. In this study we observed bacteremia rates of 0.28 and 0.25 per 1000 catheter days in the pre and post periods, respectively. These rates are lower than those observed in the rt-PA prophylaxis intervention arm of our prior trial (13), with rates of 0.40 per 1000 catheter days, and substantially lower than the heparin control arm, at 1.37 per 1000 catheter days. They are also lower than rates reported internationally from the Dialysis Outcomes and Practice Patterns Study, with rates of 2.7 per 1000 catheter days in the first month of catheter use, and 0.4 per 1000 catheter days for >12 months of catheter use. The lower rates of bacteremia that we observed may be related to the use of citrate as a locking solution. Compared with heparin, citrate has been associated with less biofilm presence and has also been shown to

Table 4.   Unadjusted mean cost of managing patients in the pre (*n*=290) and post (*n*=216) period (CAD$)

Variable	Pre Period (*n*=290), mean (SD)	Cost Difference	Post Period (*n*=216), mean (SD)
Cost of catheter locking solution	185.2 (248.4)		1843.2 (1003.0)
Cost of managing catheter malfunction	712.6 (937.8)		457.0 (790.5)
Cost of managing catheter-related bacteremia	645.5 (4750.7)		195.3 (1652.3)
Total cost	1543.3 (4864.3)		2495.5 (1900.5)
Cost difference (total post cost – total pre) (95% CI) (from bootstrapping)		962 (354 to 1571)	

95% CI, 95% confidence interval.

prevent biofilm formation (23–25), a source of infection in hemodialysis catheters (26). Another possible explanation for the lack of reduction in rates of bacteremia may be the inclusion of prevalent catheters (with established biofilm), in contrast to our prior trial that included incident catheters only. However, we are unable to draw any firm conclusions because only two of the 26 bacteremia episodes in this study occurred in patients with a duration of catheter use of <90 days. Given the small number of events (16 in the pre and ten in the post period), this study was underpowered, with only 6% power to detect a difference in our reported rates; therefore, it is not possible to draw any conclusions regarding the association between prophylactic rt-PA use and risk of bacteremia on the basis of this observational study. The systematic review by Wang *et al.* (12) noted that locking solutions of citrate, antibiotic, and rt-PA appear to reduce catheter-related bacteremia, although there were limitations in quality for most studies.

Patients undergoing hemodialysis managed with a catheter have significantly higher costs than those who have a fistula (27,28), with management of catheter malfunction and catheter-related bacteremia contributing substantially to the costs (16). We previously reported similar costs for patients managed with rt-PA/heparin and heparin alone as a locking solution (16). In our prior study we noted specifically that the higher cost of rt-PA as a locking solution was partially offset by lower costs for managing catheter-related bacteremia and rescue rt-PA for treatment of catheter malfunction in the rt-PA intervention arm. Given the similar rates of bacteremia observed in both the pre and post periods in this study, and most notably the low rates of bacteremia overall, the cost effectiveness of weekly rt-PA as a catheter locking solution is questionable at the current pricing, unless the risk of catheter-related bacteremia is lower—as observed in the prior RCT. Indeed, we found that the price of rt-PA would need to be reduced to CAD$12/ml (from the current cost of CAD$32/ml used in this study) to avoid incremental costs associated with the use of weekly rt-PA.

Our study has strengths including its prospective and pragmatic design, comparison to citrate (the most common catheter locking solution), inclusion of multiple sites, and use of analytic methods to account for repeated measures. However, our study also has important limitations, primarily due to its observational nature. First, we defined catheter malfunction on the basis of rate of rt-PA use to treat the malfunction, which may be subjective in nature

and in particular in a pre-post study design. We did, however, capture catheter stripping and removal for malfunction as a secondary outcome, although given the limited number of events we had only 15% power to detect a significant difference on the basis of our observed rates, and therefore are under-powered to draw any conclusions related to these clinically important outcomes. Second, given its observational nature, with program-wide roll-out of the intervention, blinding was not feasible. We did, however, include objective measures for secondary outcomes including bacteremia and catheter stripping and removal/replacement. Third, generalizability of results is limited to patents at high risk of catheter complications, although arguably this may be one of the most relevant and important subgroup of patients for this rt-PA strategy to be considered in; however, the proportion of patients on dialysis overall who meet this high-risk criteria is unknown. Generalizability is also limited to use of citrate as a locking solution, although rates of dysfunction are reported to be similar for both citrate and heparin locking solutions (12,29). Finally, health care costs were on the basis of data from Canada, and may vary for other countries.

In summary, we noted a significant reduction in rate of rt-PA use for treatment of catheter malfunction using once weekly rt-PA as a locking solution, compared with thrice weekly citrate (primarily) only. However, the overall use of rt-PA associated with this strategy was five-fold higher, with an incremental cost of CAD$962 per enrollment primarily accounted for by the cost of rt-PA. Our results showing a reduction in rescue rt-PA use are consistent with a prior RCT (13), although we did not observe a reduction in bacteremia or catheter stripping/removal.

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