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Prevention of Dialysis Catheter Malfunction with Recombinant Tissue Plasminogen Activator

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ABSTRACT

BACKGROUND

The effectiveness of various solutions instilled into the central venous catheter lumens after each hemodialysis session (catheter locking solutions) to decrease the risk of catheter malfunction and bacteremia in patients undergoing hemodialysis is unknown.

METHODS

We randomly assigned 225 patients undergoing long-term hemodialysis in whom a central venous catheter had been newly inserted to a catheter-locking regimen of heparin (5000 U per milliliter) three times per week or recombinant tissue plasminogen activator (rt-PA) (1 mg in each lumen) substituted for heparin at the midweek session (with heparin used in the other two sessions). The primary outcome was catheter malfunction, and the secondary outcome was catheter-related bacteremia. The treatment period was 6 months; treatment assignments were concealed from the patients, investigators, and trial personnel.

RESULTS

A catheter malfunction occurred in 40 of the 115 patients assigned to heparin only (34.8%) and 22 of the 110 patients assigned to rt-PA (20.0%) — an increase in the risk of catheter malfunction by a factor of almost 2 among patients treated with heparin only as compared with those treated with rt-PA once weekly (hazard ratio, 1.91; 95% confidence interval [CI], 1.13 to 3.22; P=0.02). Catheter-related bacteremia occurred in 15 patients (13.0%) assigned to heparin only, as compared with 5 (4.5%) assigned to rt-PA (corresponding to 1.37 and 0.40 episodes per 1000 patient-days in the heparin and rt-PA groups, respectively; P=0.02). The risk of bacteremia from any cause was higher in the heparin group than in the rt-PA group by a factor of 3 (hazard ratio, 3.30; 95% CI, 1.18 to 9.22; P=0.02). The risk of adverse events, including bleeding, was similar in the two groups.

CONCLUSIONS

The use of rt-PA instead of heparin once weekly, as compared with the use of heparin three times a week, as a locking solution for central venous catheters significantly reduced the incidence of catheter malfunction and bacteremia. (Funded by Hoffmann–La Roche; Current Controlled Trials number, ISRCTN35253449.)

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Central venous catheters are used for vascular access in the majority of patients undergoing hemodialysis.[1-3] The major complications of catheters include thrombosis and infection.[4,5] Approximately 50% of hemodialysis catheters fail within 1 year[6]; up to two thirds of the failures are due to thrombosis.[7,8] Infection related to central venous catheters is also associated with adverse health outcomes and high health care costs; indeed, catheter-related sepsis is one of the most common causes of death in patients undergoing hemodialysis.[9]

The solution instilled into the central venous catheter lumens after each hemodialysis session and left in the catheter until the next session (catheter locking solution) is used to prevent thrombosis during the period between dialysis sessions and may also prevent catheter-related infection. However, evidence supporting the use of various locking solutions to achieve these objectives is limited. Heparin has been the traditional locking solution. Several small studies have assessed whether citrate and heparin are equally efficacious for maintaining catheter patency,[10,11] but the interpretation of the results was limited because the studies had a short follow-up period and included both uncuffed and cuffed central venous catheters. Recombinant tissue plasminogen activator (rt-PA) has been used primarily to treat catheter thrombosis[12-14]; in one small randomized trial, it was shown to be superior to heparin as a locking solution.[15] The relatively high cost of rt-PA and its theoretical potential to cause bleeding, as well as the morbidity and mortality associated with catheter malfunction and infection, justify the need for more definitive evidence of the efficacy of rt-PA as a locking solution.

We performed a multicenter, randomized, blinded, controlled trial involving patients undergoing long-term hemodialysis through a newly inserted, tunneled central venous catheter to determine whether substituting rt-PA (1 mg in each lumen) for heparin once a week as a catheter locking solution, as compared with using heparin three times a week, would decrease the incidence of catheter malfunction and bacteremia.

Methods

Study Oversight

Hoffmann–La Roche funded the trial. The funding body had no role in the design or conduct of the study, in any aspect of data management or analysis, in the reporting of the study results, in the writing of the manuscript, or in the decision to submit the manuscript for publication. The trial was designed and conducted by the investigators in collaboration with the trial's steering committee (for a list of the members of the steering committee, see the Supplementary Appendix, available with the full text of this article at NEJM.org). The investigators and their research staff collected the data at each site. The University of Calgary oversaw data management and analyzed the data according to a prespecified statistical analysis plan. The protocol, including the statistical analysis plan, is available at NEJM.org. The first author and the last (senior) author attest that the study was performed in accordance with the protocol and vouch for the accuracy and completeness of the reported data.

An independent data and safety monitoring board approved the protocol and reviewed the study for safety. A planned interim analysis of safety was performed after one third of the patient-years had been accumulated (at which time 114 patients had undergone randomization) to determine whether the study should be stopped early because of safety issues; stopping the study was deemed not to be necessary.

Study Population

The study design has been described previously.[16] Briefly, adults undergoing hemodialysis in whom a tunneled catheter had been newly inserted into the upper central venous system were eligible to be included in the study if they were being treated with hemodialysis three times a week and were expected to continue undergoing hemodialysis with the use of a central venous catheter for 6 months. Major exclusion criteria were long-term receipt of systemic anticoagulant therapy, a central venous catheter inserted by means of guidewire exchange, current use of antibiotics for catheter-related bacteremia, major hemorrhage or intracranial bleeding in the previous 4 weeks, intracranial or intraspinal neoplasm, pregnancy or breast-feeding, and pericarditis. Patients with known catheter-related bacteremia could be eligible for the study once the infection had been treated and the patient had not received antibiotics for a period covering three hemodialysis sessions.

Patients were recruited at 11 Canadian sites, within 2 weeks after insertion of the catheter;

during the period before recruitment, the catheters were managed according to the usual practice at each center (Table 1 in the Supplementary Appendix). Patients were eligible for randomization after the fourth hemodialysis session if the mean blood flow was at least 300 ml per minute during sessions 3 and 4.

STUDY PROCEDURES

After providing written informed consent, eligible patients were randomly assigned, in a 1:1 ratio, by a centralized computerized service (Axiom Real-Time Metrics), with the use of a permuted-block design stratified according to center and catheter status (first hemodialysis catheter ever vs. previous use). Patients were assigned to one of two regimens for locking of the catheter after a hemodialysis session: rt-PA (1 mg in each lumen) once a week, at the midweek session, with unfractionated heparin (5000 U per milliliter, full luminal volume) used as a locking solution for the other two dialysis sessions that week, or 5000 U of unfractionated heparin per milliliter (full luminal volume) after each dialysis session. The rt-PA was administered in each lumen initially (1 mg in 1 ml), with saline added to fill the lock to the full luminal volume. The study drug (rt-PA or heparin) was prepared and dispensed by the pharmacy in such a way that concealment of the treatment assignments was ensured, with four syringes prepared per patient for administration of the locking solution. On the days on which heparin was used for all the patients, the heparin was prepared and administered by the hemodialysis nurse according to the usual standard of care.

Patients were followed for 6 months after they underwent randomization. Patients who met the criteria for the primary outcome were followed for at least 1 month after the primary outcome occurred and continued to be followed until one of the following occurred: the patient underwent six consecutive successful hemodialysis sessions (mean blood flow, ≥300 ml per minute during each treatment), 3 months elapsed, or the central venous catheter was no longer used. The follow-up period for these patients was extended so that the natural history of malfunction of the central venous catheter could be documented and the costs associated with maintaining patency could be assessed, for use in the economic analysis. We included six consecutive successful hemodialysis sessions as part of the definition of the extended follow-up period because a second malfunction typically occurs within 2 weeks after the initial malfunction.[17]

OUTCOMES

The primary outcome was catheter malfunction, which was defined as the first occurrence of any of the following, after attempts to reestablish patency had been undertaken (see Table 2 in the Supplementary Appendix): peak blood flow of 200 ml per minute or less for 30 minutes during a dialysis treatment, mean blood flow of 250 ml per minute or less during two consecutive dialysis treatments, or inability to initiate dialysis owing to inadequate blood flow. The definition of catheter malfunction was chosen by the study investigators on the basis of published guidelines.[18] Catheter malfunction was selected as the primary outcome because of concern that recruitment would be limited if the sole outcome were removal of the central venous catheter and because poor blood flow during dialysis is associated with adverse outcomes.[19]

Catheter-related bacteremia was defined according to published criteria,[16,20] with both "definite" and "probable" infections included in the outcome (Table 3 in the Supplementary Appendix). Bacteremia was treated by the attending nephrologist; patients remained in the study and were followed for the primary outcome. If a new central venous catheter was clinically indicated, the patient's data were censored at the time of removal of the initial central venous catheter.

Bleeding was classified as fatal bleeding, major bleeding (bleeding at a critical site or overt bleeding with a fall in the hemoglobin level of 20 g per liter or more or requiring transfusion of 2 or more units of packed red cells), clinically important nonmajor bleeding (overt bleeding requiring admission to the hospital or a visit to a medical facility or overt bleeding leading to an intervention such as suturing), or minor bleeding (all other episodes of bleeding).

STATISTICAL ANALYSIS

We estimated that with a total of 340 participants (170 in each group), the study would have 80% power to detect approximately a 34% reduction in the incidence of catheter malfunction with rt-PA once weekly, assuming a 1-year rate of catheter malfunction of 95% in the heparin group and an annual dropout rate of 75% (on the basis

of data from the University Health Network, Toronto [unpublished data] and Little and Walshe[17]), at a two-sided alpha level of 0.05.[16] Because enrollment was slower than expected, an interim analysis that was based on the overall event rate (with the group assignments concealed) was performed after 197 patients had undergone randomization, to determine what power the study would be expected to have if 225 patients were enrolled. This analysis showed that the study would have 80% power with the event rate at that point and an anticipated effect size of 50%. Therefore, enrollment was halted after 225 patients had undergone randomization.

Survival curves for the primary and secondary outcomes were prepared with the use of the Kaplan–Meier method and were compared with the use of a two-sided log-rank test. Cox proportional-hazards models were used to compare event-free survival in the rt-PA and heparin groups, stratified according to center and catheter status. The results of analyses with models that included terms for the interaction between treatment and the stratification variables were nonsignificant; therefore, the results for the overall study population are presented. Comparisons of primary and secondary outcomes were based on the treatment assignments, irrespective of adherence to the intervention. We also performed a secondary analysis according to the actual treatment received. Follow-up data were censored at the end of the study (January 15, 2010) or at the time of death, a switch to an alternative form of renal-replacement therapy, removal of the central venous catheter or use of an alternative dialysis access, or the patient's transfer to a clinical center that was not involved in the trial — whichever came first. Statistical analyses were performed with the use of SAS, version 9.2 (SAS Institute) or Stata, version 11.1 (Stata) software. All reported P values are two-sided and have not been adjusted for multiple testing.

Although a full economic evaluation for this trial is not yet complete (administrative data on the cost of hospitalizations are not yet available), we provide a preliminary analysis of cost-effectiveness, on the basis of the cost (in Canadian dollars, as of 2010) of the interventions ($64 for 2 mg of rt-PA and $1.25 for 10,000 U of heparin) and the estimated cost of treating patients in whom bacteremia develops or catheter malfunction occurs. The cost of removal and replacement of a catheter ($1,228), and the mean cost of outpatient and inpatient treatment for catheter-related bacteremia ($485 and $6,040, respectively) were estimated from a detailed cost analysis of hemodialysis vascular access.[21]

RESULTS

STUDY POPULATION

We assessed 2325 patients for eligibility, of whom 225 underwent randomization; 110 patients were assigned to receive rt-PA, and 115 were assigned to receive heparin only (Fig. 1). All the patients received their assigned intervention except for one patient in the rt-PA group, who underwent emergency surgery before the first dose of the study drug was administered. The baseline characteristics of the two groups were similar (Table 1, and Table 4 in the Supplementary Appendix).

A total of 58 patients in the rt-PA group (52.7%) and 56 in the heparin group (48.7%) discontinued the study medication before the end of the 6-month study period. The median duration of follow-up was 115.5 days in the rt-PA group and 89.0 days in the heparin group. No patients were lost to follow-up.

PRIMARY OUTCOME

The primary outcome occurred in 62 patients — 22 (20.0%) in the rt-PA group and 40 (34.8%) in the heparin group (hazard ratio with heparin vs. rt-PA, 1.91; 95% confidence interval [CI], 1.13 to 3.22; P=0.02) (Fig. 2). There was no significant interaction between catheter status (first hemodialysis catheter ever vs. previous use) and treatment assignment (P=0.84) or between clinical center and treatment assignment (P=0.46). The results were unchanged in a model adjusted for catheter status and clinical center (hazard ratio with heparin, 1.88; 95% CI, 1.11 to 3.19) and in a sensitivity analysis with a composite outcome of catheter malfunction or early discontinuation of the study intervention (Fig. 1 in the Supplementary Appendix). A total of 31 patients (50.0%) met the criteria for the primary outcome because of a peak blood flow of 200 ml per minute or less for 30 minutes, 19 patients (30.6%) because of an inability to initiate dialysis, and 12 patients (19.4%) because of a mean blood flow of 250 ml per minute or less for two consecutive sessions.

The results were similar in a secondary analysis that was performed according to the actual

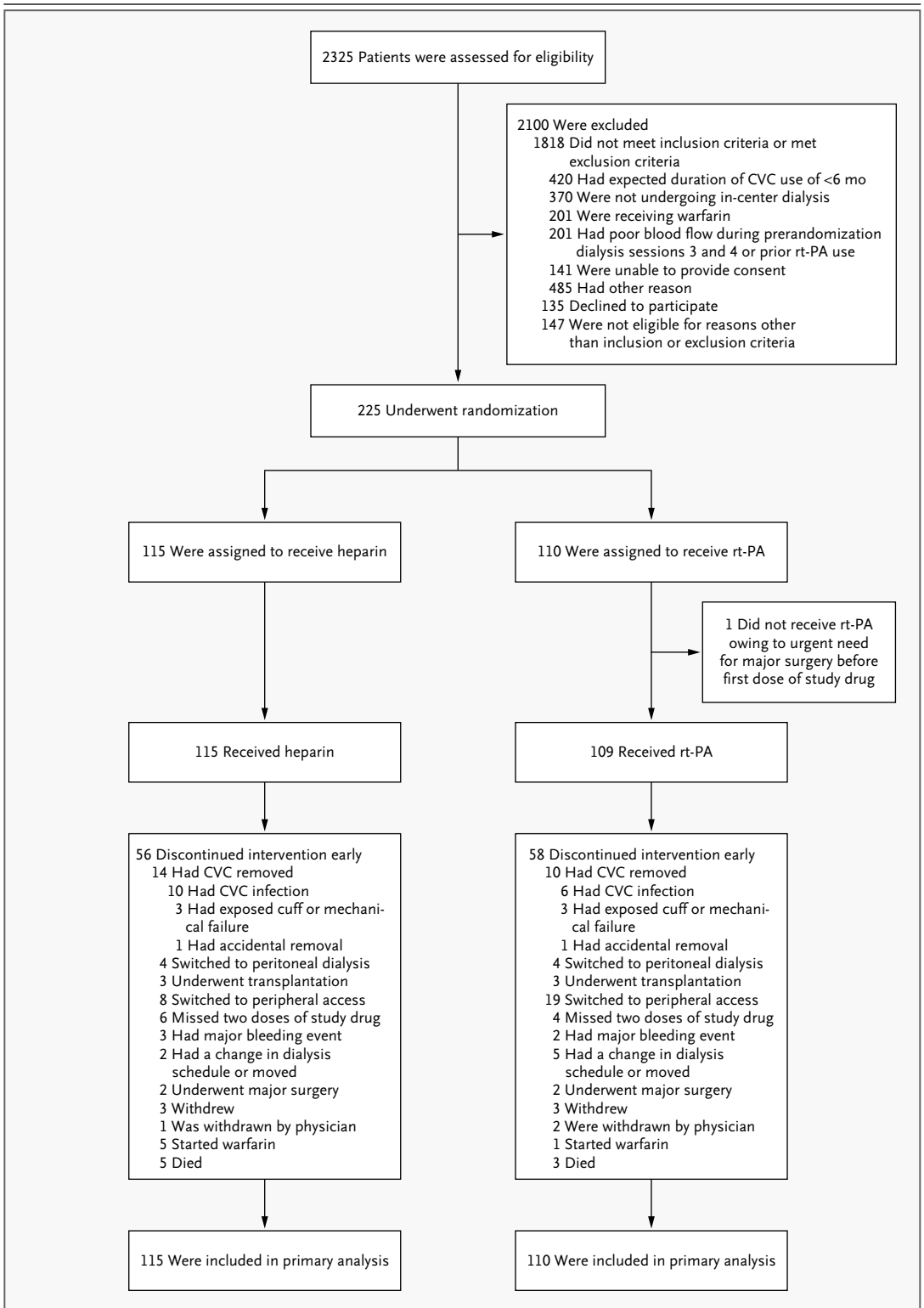


Figure 1. Screening, Randomization, and Follow-up.

CVC denotes central venous catheter, and rt-PA recombinant tissue plasminogen activator.

Table 1. Baseline Characteristics of the Study Patients.*

Characteristic	rt-PA Group (N=110)	Heparin-Only Group (N=115)	P Value†
Age — yr	61.6±16.6	64.8±15.2	0.13
Female sex — no. (%)	39 (35.5)	49 (42.6)	0.27
First dialysis catheter ever — no. (%)	67 (60.9)	70 (60.9)	0.99
Indication for current central venous catheter — no. (%)			0.34
Starting dialysis without peripheral access	60 (54.5)	58 (50.4)	
Failure of peripheral access or awaiting peripheral access	21 (19.1)	27 (23.5)	
Catheter-related infection	4 (3.6)	10 (8.7)	
Transfer from peritoneal dialysis or failed kidney transplantation	13 (11.8)	8 (7.0)	
Other	12 (10.9)	12 (10.4)	
Cause of end-stage renal disease — no. (%)			0.38
Diabetic nephropathy	38 (34.5)	33 (28.7)	
Glomerulonephritis	10 (9.1)	7 (6.1)	
Polycystic kidney disease	3 (2.7)	3 (2.6)	
Hypertension or vascular disease	15 (13.6)	27 (23.5)	
Other	44 (40.0)	45 (39.1)	
Duration of dialysis — yr			0.43
Median	0.5	1.0	
Interquartile range	0.0–1.0	0.0–6.0	
Coexisting or prior illnesses — no. (%)			
Diabetes mellitus	60 (54.5)	64 (55.7)	0.87
Ischemic heart disease	26 (23.6)	21 (18.3)	0.32
Congestive heart failure	28 (25.5)	22 (19.1)	0.25
Cerebral vascular disease	12 (10.9)	17 (14.8)	0.30
Hypertension	104 (94.5)	102 (88.7)	0.12
Prior pulmonary embolism or deep-vein thrombosis	5 (4.5)	6 (5.2)	0.82
Prior gastrointestinal bleeding	12 (10.9)	9 (7.8)	0.43
Medications — no. (%)			
Aspirin	53 (48.2)	57 (49.6)	0.43
Other antiplatelet agent	12 (10.9)	9 (7.8)	0.19
Serum albumin — g/liter	31.8±5.8	32.3±7.1	0.57
Hemoglobin — g/liter	106.0±16.0	106.1±15.5	0.96
Platelet count — $\times 10^{-9}$/liter	247.5±92.2	254.4±113.2	0.62
International normalized ratio	1.1±0.1	1.1±0.1	1.00

* Plus–minus values are means ±SD.
† P values for mean data were calculated with the use of Student's t-test, P values for percentages with the use of the chi-square test or Fisher's exact test, and P values for medians with the use of the Wilcoxon rank-sum test.

treatment received. The primary outcome occurred in 54 participants: 18 (16.4%) in the rt-PA group and 36 (31.3%) in the heparin group (hazard ratio with heparin, 2.13; 95% CI, 1.20 to 3.76).

Among patients in whom the primary outcome occurred, immediate management of the central venous catheter included reversal of catheter lines (in 13 of 22 patients in the rt-PA group [59.1%] and 14 of 40 in the heparin group [35.0%]; P=0.07) and use of rt-PA (in 4 of 22 patients in the rt-PA group [18.2%] and 20 of 40 in the heparin group [50.0%]; P=0.01). One pa-

tient in the heparin group underwent an immediate exchange of the central venous catheter.

SECONDARY OUTCOME

Catheter-related bacteremia (which was classified as definite, according to the published criteria used, in 45.0% of the cases) occurred in 5 patients (4.5%) assigned to receive rt-PA and 15 patients (13.0%) assigned to receive heparin alone (hazard ratio with heparin, 3.30; 95% CI, 1.18 to 9.22; P=0.02) (Fig. 3). This corresponded to rates of 0.40 and 1.37 episodes of bacteremia per 1000 patient-days in the rt-PA and heparin groups, respectively (P=0.02).

FOLLOW-UP AFTER THE PRIMARY OUTCOME

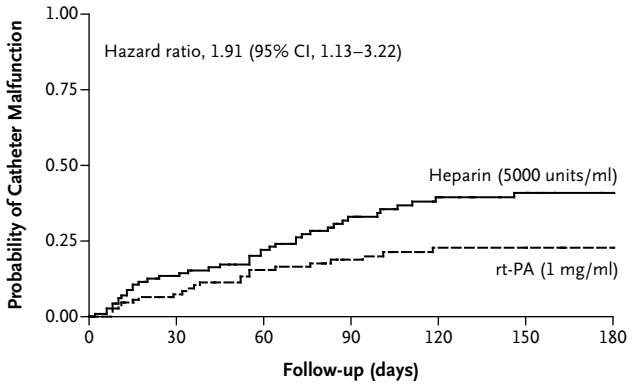
Patients who met the criteria for the primary outcome were followed for up to 3 months or until removal of the catheter, with a median follow-up period that covered 11.5 and 10.0 dialysis sessions in the rt-PA and heparin groups, respectively. Treatment with rt-PA (outside the study protocol) for repeat malfunction of the original catheter occurred in 8.8% of the sessions (32 of 364 sessions) in the rt-PA group and 12.8% of the sessions (101 of 792 sessions) in the heparin group (P=0.06) (see also Table 5 in the Supplementary Appendix).

ADVERSE EVENTS

Serious adverse events were reported in 23 patients (20.9%) receiving rt-PA and 34 (29.6%) receiving heparin (P=0.14) (Table 2). The rate of adverse events was similar in the two groups: 70.0% (77 of 110 patients) in the rt-PA group and 68.7% (79 of 115 patients) in the heparin group (P=0.83). Most patients had multiple events, with the result that there was a total of 454 adverse events and 68 serious adverse events. Neither the frequency nor the severity of bleeding events was greater among patients in the rt-PA group than among patients in the heparin group. There were 4 intracranial bleeding episodes, all in patients in the heparin group; 1 episode was a fatal brain-stem hemorrhage. There were no intracranial bleeding episodes or deaths caused by bleeding in the rt-PA group.

COST-EFFECTIVENESS ANALYSIS

For each patient who received therapy for 6 months, the mean costs (in Canadian dollars) of rt-PA and heparin were $1,794 and $195, respectively; the cost of managing complications associated with catheter malfunction and catheter-related bacteremia per patient was $156 with rt-PA and $582 with heparin. Thus, the incremental cost of caring for patients with rt-PA as compared with heparin was $1,173 per patient, or $13,956 per episode of catheter-related bacteremia prevented.



No. at Risk (No. with Catheter Malfunction)

Heparin	115	(15)	92	(9)	79	(10)	57	(5)	45	(1)	38	(0)	32
rt-PA	110	(8)	96	(8)	80	(3)	66	(3)	53	(0)	50	(0)	45

Figure 2. Kaplan–Meier Curves for the Time to Catheter Malfunction, According to Study Group.

The numbers in parentheses below the x axis are the numbers of patients in whom an episode of catheter malfunction occurred in the interval between follow-up assessments. The hazard ratio is for the group that received heparin as compared with the group that received recombinant tissue plasminogen activator (rt-PA).

DISCUSSION

As compared with the use of unfractionated heparin three times a week, the use of rt-PA as a catheter locking solution once a week (with heparin used the other two times) significantly decreased the incidence of catheter malfunction and bacteremia among patients with a newly inserted hemodialysis catheter. The findings were consistent between patients for whom this was the first use of a catheter and those who had had previous catheters. The frequency of bleeding or other serious adverse events was not increased with the use of rt-PA.

Catheter thrombosis occurs at a frequency of 0.5 to 3.0 events per 1000 catheter-days,[4,22] resulting in shortened dialysis treatments, less-than-adequate dialysis, and increased morbidity and mortality.[19] Thrombolytic agents are used to treat catheter malfunction in both nondialysis

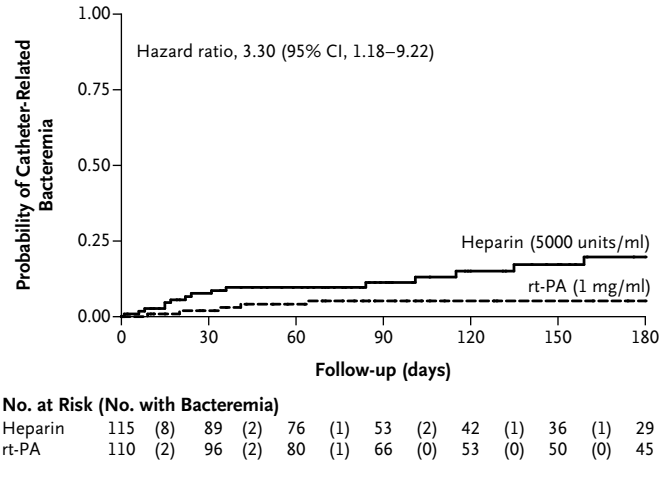


Figure 3. Kaplan–Meier Curves for the Time to a First Episode of Bacteremia, According to Study Group.

The numbers in parentheses below the x axis are the numbers of patients in whom a first episode of catheter-related bacteremia developed in the interval between follow-up assessments. The hazard ratio is for the group that received heparin as compared with the group that received recombinant tissue plasminogen activator (rt-PA).

catheters[23,24] and dialysis catheters.[12,13] Thrombolytic agents such as rt-PA preferentially bind to fibrin and activate plasminogen in close proximity to the clot to form plasmin, which dissolves the fibrin in the clot and prevents fibrinogen from forming more fibrin. The binding of rt-PA to fibrin confines fibrinolysis to the thrombus, theoretically averting systemic activation and justifying the use of this drug for the treatment and prevention of catheter malfunction.

Evidence to guide the use of locking solutions for the primary prevention of catheter malfunction has been based on studies in the critical care and oncology settings.[25-27] It was uncertain whether these results could be generalized to catheters used for hemodialysis, which are larger, are used for longer periods, and require locking solutions to remain in place for up to 72 hours. A single randomized, crossover trial involving 12 patients undergoing hemodialysis showed that locking with 2 mg of rt-PA in each catheter lumen was superior to locking with heparin.[15] Our results are consistent with these findings and indicate that the use of rt-PA as a locking solution at a reduced dose (1 mg in each lumen) and a reduced frequency (once a week) decreases the rates of catheter malfunction and bacteremia, although the number of catheters removed because of malfunction was small.

A few trials have evaluated other strategies for the primary prevention of catheter malfunction. A fixed dose (1 mg) of warfarin was shown to be ineffective for the prevention of catheter malfunction.[28] The rates of catheter malfunction with 30% trisodium citrate were similar to those with heparin, although there was a reduction in catheter-related bacteremia in the citrate group.[11]

Catheter-related bacteremia is a serious complication, with an incidence of 2.5 to 6.5 episodes per 1000 catheter-days.[5,29] Furthermore, septicemia is responsible for more than 75% of deaths from infection among patients undergoing dialysis.[9] Several mechanisms may contribute to catheter-related bacteremia, including the formation of an intraluminal thrombosis, which may act as a nidus for the development of bacterial biofilm.[30,31] Although antibiotic locking solutions have been proposed for the treatment[32] or prevention[33,34] of bacteremia, side effects limit their widespread use.[35] Although the interpretation of our results is limited by the small number of events, we found that the risk of bacteremia was increased by a factor of 3 in the heparin-only group as compared with the rt-PA group. Furthermore, the number of central venous catheters that were removed in both groups owing to an episode of presumed or confirmed bacteremia was not inconsequential. Although an earlier trial suggested that there was a reduction in the rate of bacteremia with 30% trisodium citrate as compared with heparin,[11] two recent trials of 46.7% sodium citrate[36] and taurolidine–citrate[37] did not show any significant difference. Since management of catheter-related bacteremia is expensive and often requires replacement of central venous catheters, our finding that rt-PA reduces the risk of this complication without increasing the risk of bleeding is potentially very important.

Though our study is a relatively large, multicenter trial with complete follow-up data, it has several limitations. First, although our primary outcome was defined according to published guidelines,[18] it was a surrogate outcome that was based on measurement of blood flow. Ongoing evidence of catheter malfunction after the primary outcome provides support for the validity of this definition. Second, we discontinued enrollment early, owing to difficulties with patient

Table 2. Adverse Events.*

Event	rt-PA Group (N=110)	Heparin-Only Group (N=115)	P Value†
	no. (%)		
Any serious adverse event	23 (20.9)	34 (29.6)	0.14
Bleeding			0.93
Minor	7 (6.4)	9 (7.8)	
Clinically important nonmajor	3 (2.7)	2 (1.7)	
Major	3 (2.7)	4 (3.5)	
Fatal	0	1 (0.9)	
Hospitalization			0.15
For ischemic heart disease	3 (2.7)	5 (4.3)	
For congestive heart failure	3 (2.7)	0	
For arrhythmia	2 (1.8)	0	
For cerebrovascular disease	1 (0.9)	2 (1.7)	
For infection			
Related to central venous catheter	2 (1.8)	4 (3.5)	
Not related to central venous catheter	5 (4.5)	3 (2.6)	
For bleeding event	1 (0.9)	3 (2.6)	
For other event	8 (7.3)	18 (15.7)	
Death			0.72
Cardiovascular-related	1 (0.9)	0	
Infection-related	1 (0.9)	1 (0.9)	
Bleeding-related	0	1 (0.9)	
Other‡	1 (0.9)	3 (2.6)	

* Adverse events were reported until 30 days after the last dose of study medication was administered.
† P values were calculated with the use of the chi-square test or Fisher's exact test.
‡ Other deaths in the heparin group were related to withdrawal of treatment, perforated bowel, and metastatic cancer (1 patient each); the other death in the rt-PA group occurred at home from complications of end-stage renal disease.

recruitment. However, even the smaller sample had adequate power to detect a significant difference in both primary and secondary outcomes. Third, because of protocol-mandated selection criteria, we were not able to perform analyses in potentially important subgroups, such as patients in whom the expected duration of use of a central venous catheter was less than 6 months. Finally, a large proportion of patients discontinued the study medication during the course of the study (often because of a switch to arteriovenous access or hospitalization), as has been observed in previous trials involving patients undergoing hemodialysis.[38]

In conclusion, we found that among patients undergoing hemodialysis, rt-PA administered once a week as a catheter locking solution (with heparin administered the other two times), as compared with heparin administered three times a week, led to a significant reduction in the incidence of both catheter malfunction and bacteremia.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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