Urokinase-containing locking solution in the prevention of dialysis catheter dysfunction: a double blind randomized controlled trial

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ABSTRACT

Introduction: The prophylactic use of recombinant tissue plasminogen activator once weekly reduces the incidence rate of tunneled cuffed catheter (TCC) malfunction and bacteremia as compared to the exclusive use of heparin as locking solution. Restricting the use of prophylactic thrombolytic agents to patients with a history of thrombotic TCC malfunction could be more cost effective. We conduct a multicenter, double-blind, randomized controlled trial and test the hypothesis that weekly use of urokinase lock will reduce the incidence of thrombotic malfunction by 50% in prevalent hemodialysis patients with a history of thrombotic malfunction.

Methods: Patients with a history of at least two separate TCC thrombotic dysfunctions treated with urokinase lock during the 6 months preceding inclusion are recruited in eight Belgian dialysis units. Patients are randomized in two groups: the control group receiving Taurolock™-HEP500 (heparin 500 IU/mL, taurolidine, citrate 4%) after each hemodialysis session and the treatment group receiving Taurolock-U 25,000 (urokinase 25,000, taurolidine, citrate 4%) once a week and the standard Taurolock-HEP500 at the end of the two others sessions. The primary outcome is the incidence rate of TCC thrombotic dysfunction defined by the use of urokinase. The secondary outcomes are the incidence rate of TCC removal and systemic thrombolysis. For the study, both patients and healthcare staff are blinded to treatment allocation.

Conclusions: The present trial is the first to investigate the effect of Taurolock-U 25,000 catheter lock once a week as secondary prevention in hemodialysis patients with the highest risk of TCC-related thrombotic dysfunction.

Trial registration: ClinicalTrials.gov Identifier: NCT02036255

Keywords: Catheter obstruction, Renal dialysis, Thrombolytic therapy, Urokinase
thrombotic malfunction, with available data rather pointing at non-inferiority of heparin lock in this indication (6-11).

The comparison of these studies based on blood flow remains limited by the lack of a standardized definition of TCC-related thrombotic dysfunction. Recombinant tissue plasminogen activator (rt-PA) is the only locking solution which significantly reduces catheter malfunction as compared to heparin locks. Indeed, Hemmelgarn et al showed that the prophylactic use of rt-PA once weekly reduces the incidence rate of TCC malfunction and bacteremia as compared to the exclusive use of heparin as locking solution (12). However, the systematic use of thrombolytic agents is costly and probably does not provide a benefit to the large proportion of patients with a low propensity for thrombosis and very low risk of thrombotic TCC malfunction when treated with standard catheter locks. A more cost-effective approach might therefore consist of the restriction of prophylactic thrombolytic agents to patients with a documented history of thrombotic TCC malfunction.

Currently, our policy for TCC management involves the use of a routine locking solution containing taurolidine, citrate 4% and heparin (Taurolock™-HEP500, Tauro-Implant, Winsen, Germany – www.tauro-implant.de) after each hemodialysis session. In case of TCC thrombotic malfunction (defined in the Methodology and Supplementary Material, available online at www.vascular-access.info), urokinase (Actosolv™, Eumedica, www.eumedica.com) is employed as thrombolytic agent to restore the patency of the TCC. The objective of the present multicenter, randomized, double-blinded placebo-controlled trial is to investigate whether the substitution of the standard locking solution with a locking solution containing taurolidine and urokinase once a week (Taurolock-U 25,000-www.taurolock.com) reduces the rate of TCC thrombotic dysfunction requiring urokinase therapy by at least 50% in hemodialysis patients with a documented history of TCC malfunction.

Methods/design

Study design

Prospective, multicenter, randomized, placebo-controlled trial with blinding of patients, health-care providers and all study staff. We conduct this study in accordance with the ethical principles of the Declaration of Helsinki and according to the rules and guidelines of Good Clinical Practice. The study is approved by the Ethic Committee of each participating center. A synopsis of the study design can be found on clinicaltrials.gov (https://clinicaltrials.gov/ct2/show/NCT02036255).

Study population

Inclusion criteria

The study includes prevalent adult patients undergoing HD at least three times a week via a TCC used for at least 3 months. To be eligible, the current TCC must have presented thrombotic dysfunction with requirement for therapeutic thrombolytic therapy with urokinase on at least two separate occasions during a maximum time interval of 6 months preceding inclusion. Provided the same TCC is used for at least 3 months, the patient can be included as soon as two separate thrombotic dysfunctions treated with urokinase have occurred, even if the total period covering the administration of the two locks is less than 6 months.

Inclusion into the trial is only permitted if the last therapeutic thrombolytic locking solution has been administered more than three dialysis sessions (one week) earlier and adequate catheter function has been restored. Patients are recruited at eight Belgian dialysis units.

Exclusion criteria

Exclusion criteria included the following: a history of heparin-induced thrombocytopenia, presence of a femoral TCC, established intolerance for the taurolidine locking solution (citrate, taurolidine, heparin) or for urokinase, administration of antibiotics for ongoing TCC-related infection (exit site or bacteremia) which ended less than one week before inclusion, or scheduled holidays for more than 2 weeks during the 6-month study period. Patients with TCC dysfunction due to mechanical problems such as kinking, TCC migration, misplacement, inadequate length and patient malposition were also excluded.

Study procedures

After providing written informed consent, eligible patients start with a run-in period of three successive dialysis sessions during which the absence of thrombotic TCC dysfunction or TCC-related infection are clinically verified. Baseline blood flow is defined as the mean of the average blood flows during the three consecutive dialysis sessions of the screening period. The mean blood flow of each dialysis session is calculated as the total blood volume processed in milliliters divided by the time on dialysis in minutes. Inclusion into the trial depends on the results of the screening process, and the following conditions have to be fulfilled.

- mean TCC blood flow is higher than 250 mL/min with pre-pump arterial pressure > -250 mmHg and post-pump venous pressure <=250 mmHg during each dialysis session
- no current need for thrombolytic locking solution (urokinase)
- absence of TCC-related infection (exit-site infection or bacteremia).

Patients with a history of TCC-related infection can be included if the infection has been successfully treated, did not require TCC removal and antibiotics have been stopped for at least three dialysis sessions prior to inclusion.

Similarly, patients with catheters who initially did not reach the attended minimal TCC blood flow and/or needed urokinase during the screening period, can be rescreened and eventually included if they fulfill inclusion criteria at that time. All patients fulfilling the inclusion criteria in terms of thrombotic dysfunction and urokinase treatments are recorded in a screening log. Reasons for screening failure or other causes of non-inclusion are recorded in the log according to the latest CONSORT guidelines.
Inclusion procedure

For each eligible patient, the sub-investigators at the local centers send e-mail or a fax to the principal investigator and the clinical nurse of the UZ Brussels hospital. This includes patient ID, the center ID and confirmation that inclusion and exclusion criteria are fulfilled and that the informed consent is signed.

Randomization procedure

Patients are allocated either to the intervention or to the control group using block randomization with permuted blocks of four stratified for the participating centers.

The pharmacist of the central site performs the allocation and assigns a kit number to the patient. The principal investigator and pharmacist at the local site are informed of this kit number by mail by the pharmacist of UZ Brussels. The box with a sealed envelope is shipped to the site. Each box contains 30 doses of blinded product with identical kit number for a single patient. Each vial and ampoule is labeled and this removable label must be pasted on the medication log form for each patient and completed with the date of administration.

Blinding procedure

Physicians, dialysis nurses, patients and study coordinators of each center are blinded for the allocation. Both active treatment and placebo are delivered in identical vials and ampoules. The final product also looks identical. Taurolock-U 25,000 and the corresponding placebo are kept at the central hospital pharmacy of the UZ Brussels until shipment to the participating dialysis unit after randomization.

If a medical emergency occurs and a decision regarding the subject’s condition requires knowledge of the treatment assignment, the study blind may be broken for the specific subject.

Intervention

Administration of the study medication: when a new patient is included, the hospital pharmacy of the Universitair Ziekenhuis Brussel prepares blinded locking solutions sufficient for 6 months of treatment and dispenses them to the participating centers. For patients allocated to the intervention arm, the Taurolock-U 25,000 is administered once weekly on a fixed day, i.e., the day before the longest dialysis-free interval (Friday or Saturday depending on the patient’s schedule). Urokinase is delivered in a separate vial and dissolved with the content of an ampoule containing citrate and taurolidine just before use. The control group receives an identical placebo powder containing the excipients of the urokinase preparation without urokinase. This placebo powder is dissolved in the classical Taurolock-HEP500 locking solution. The excipients (glycine, etc.) have no known effect on Taurolock-HEP500. The Taurolock-HEP500 administered after the first and second dialysis session of the week is for both treatment and placebo group the regular commercially available product with commercial labeling. If a patient needs an extra dialysis session during the week, he receives the classical locking solution (Taurolock-HEP500) from the stock of the center at the end of that session.

The study medication must be stored between 2-25°C. The storage room temperature is monitored in each participating center. At the end of the study, all used and unused medication must be accounted for by means of a study agent accountability form.

Outcomes

The primary outcome is the median number of TCC thrombotic malfunction episodes requiring therapeutic thrombolytic locking solution at the end of the follow-up.

The present protocol defines thrombotic TCC dysfunction as the occurrence of one or more of the following events:

- The occurrence during 2 consecutive dialysis sessions of a mean blood flow lower than 85% of the average blood flow measured during the three dialysis sessions before inclusion, not resolved by patient repositioning or TCC flushing, and persistent after switching of the arterial and venous blood lines. Blood flow has to be maintained with pre-pump arterial pressure superior to -250 mmHg and/or post-pump venous pressure lower than +250 mmHg.
- The inability to initiate dialysis due to complete occlusion of at least one line of the catheter (late manifestation).

In case of an accidentally missed urokinase administration, the patient should receive the therapeutic urokinase on the next dialysis session, independently of the mean blood flow observed at this moment.

In a pre-specified subgroup analysis, the study will also investigate whether gender, history of previous venous thromboembolism (deep vein thrombosis [DVT], pulmonary embolism and/or AVF/graft failure due to thrombosis) and use of anticoagulation or antiplatelet therapy have an effect on the efficacy of Taurolock-U 25,000 in the prevention of TCC-related thrombotic dysfunction.

The following secondary outcomes will be assessed

- Removal of the TCC (assessed as proportion of patients with removal of the catheter and as time to removal of the catheter). Effect of the intervention will be assessed for catheter removals for any cause as well as for removals due to thrombosis or infection.
- Proportion of catheters receiving systemic thrombolytic therapy because of thrombosis resistant to treatment with therapeutic urokinase locking solution.
- Catheter-related bloodstream infections (CRB) — according to Centers for Disease Control (CDC) definitions (13, 14) (Tab. I) and exit-site infections.

No blood samples are to be systematically obtained for bacteriologic analyses during the study. Only patients with fever, chills, and/or biological inflammatory syndrome are to be evaluated by blood cultures. Data of TCC exit-site infection are also to be collected.
Participant timeline

Duration of the study

The duration of the study is 6 months starting from the moment of randomization. Currently, the study randomization process is completed and some patients are still active.

Withdrawal from the study

Patients can withdraw from the study either by withdrawal of consent or by request from the investigator.

Removal of catheter secondary to any cause, treatment of catheter thrombosis with systemic thrombolytic therapy, administration of an antibiotic-containing locking solution during 3 weeks in case of CRB, withdrawal of consent, renal transplantation, use of an arteriovenous fistula (AVF) or a graft, transfer to peritoneal dialysis (PD) or to another center, patient death and loss to follow-up exclude the patient from further follow-up in the study.

If the study medication is stopped, although the patient is continuing hemodialysis treatment with the catheter, data concerning study outcomes should continue to be collected in order to allow analysis of the patient according to the intention-to-treat principle.

Systemic thrombolytic therapy for thrombotic catheter dysfunction

The participating hemodialysis units have different approaches to manage TCC thrombotic dysfunction that is resistant to three consecutive administrations of therapeutic urokinase locks. Some centers change the dysfunctional TCC while other centers administer systemic thrombolysis in case clotting around the catheter tip was shown after pacification of the superior vena cava. To avoid bias in the follow-up of patients in different centers, the administration of systemic thrombolysis is considered as an intervention equivalent to catheter replacement and terminates follow-up in the study.

Data collection

Baseline data and ongoing data collection are recorded after each dialysis session by the local investigators in a patient record book (Tabs II. and III).

For each included patient, the mean blood flow has to be calculated at the end of the dialysis session (within the 5 last minutes as the ratio of the blood volume treated/dialysis time in minutes) and to be compared to the baseline TCC function to evaluate the need of urokinase administration.

Monthly laboratory data

Hemoglobin, platelets, albumin, CRP

Monitoring of dialysis efficacy (URR and single pool Kt/V)

TCC = tunneled cuffed catheter; AVF = arteriovenous fistula; DVT = deep vein thrombosis; EPO = erythropoietin; CRP = C-reactive protein; URR = urea reduction ratio.

TABLE I - Definition for tunneled cuffed catheter-related bacteremia

<table>
<thead>
<tr>
<th>Definite bacteremia</th>
<th>Probable bacteremia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septic thrombophlebitis with a single positive blood culture, or</td>
<td>Two or more positive blood cultures with no evidence for source other than catheter, or</td>
</tr>
<tr>
<td>Single positive blood culture and positive culture of catheter segment with identical organism, or</td>
<td>Single positive blood culture for <em>S. aureus</em> or <em>Candida</em> with no evidence for source other than catheter, or</td>
</tr>
<tr>
<td>10-fold colony count difference in blood cultures drawn from catheter and peripheral blood, or</td>
<td>Single positive blood culture for coagulase-negative <em>Staphylococcus, Bacillus, Corynebacterium, Enterococcus</em> in immunocompromised or neutropenic patients or in patients receiving TPN with no evidence for source other than catheter defervescence of symptoms after antibiotic therapy with or without removal of catheter, in the setting in which blood cultures confirm infection, but catheter tip does not (or catheter tip does, but blood cultures do not) in a symptomatic patient with no other apparent source of infection</td>
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<tr>
<td>Single positive blood culture and positive culture from discharge or aspirate from exit-site, tunnel or pocket with identical organism in a symptomatic patient with no other apparent source of infection</td>
<td></td>
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</tbody>
</table>

TABLE II - Baseline characteristics of the patient population and ongoing data collection

<table>
<thead>
<tr>
<th>Baseline data</th>
<th>Monthly laboratory data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, sex, origin, duration on dialysis, cause of renal failure</td>
<td>Hemoglobin, platelets, albumin, CRP</td>
</tr>
<tr>
<td>Type of TCC, date of placement, localization, history of TCC removal for thrombosis or for bacteremia</td>
<td>Monitoring of dialysis efficacy (URR and single pool Kt/V)</td>
</tr>
<tr>
<td>History of AVF/graft failure due to thrombosis</td>
<td></td>
</tr>
<tr>
<td>Comorbidity (diabetes, hypertension, ischemic cardiomyopathy, peripheral arteriopathy, active neoplasm, venous thromboembolism: DVT, pulmonary embolism)</td>
<td></td>
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<tr>
<td>Medication use: anticoagulation, antplatelet agent</td>
<td></td>
</tr>
<tr>
<td>Hemodialysis modality, time on dialysis (min), weight loss, target weight</td>
<td></td>
</tr>
<tr>
<td>EPO dose per week (UI/kg/week)</td>
<td></td>
</tr>
<tr>
<td>Anticoagulation on dialysis, mean heparin dose</td>
<td></td>
</tr>
</tbody>
</table>

Participant timeline

Duration of the study

The duration of the study is 6 months starting from the moment of randomization. Currently, the study randomization process is completed and some patients are still active.

Withdrawal from the study

Patients can withdraw from the study either by withdrawal of consent or by request from the investigator.

Removal of catheter secondary to any cause, treatment of catheter thrombosis with systemic thrombolytic therapy, administration of an antibiotic-containing locking solution during 3 weeks in case of CRB, withdrawal of consent, renal transplantation, use of an arteriovenous fistula (AVF) or a graft, transfer to peritoneal dialysis (PD) or to another center, patient death and loss to follow-up exclude the patient from further follow-up in the study.

If the study medication is stopped, although the patient is continuing hemodialysis treatment with the catheter, data concerning study outcomes should continue to be collected in order to allow analysis of the patient according to the intention-to-treat principle.

Systemic thrombolytic therapy for thrombotic catheter dysfunction

The participating hemodialysis units have different approaches to manage TCC thrombotic dysfunction that is resistant to three consecutive administrations of therapeutic urokinase locks. Some centers change the dysfunctional TCC while other centers administer systemic thrombolysis in case clotting around the catheter tip was shown after pacification of the superior vena cava. To avoid bias in the follow-up of patients in different centers, the administration of systemic thrombolysis is considered as an intervention equivalent to catheter replacement and terminates follow-up in the study.

Data collection

Baseline data and ongoing data collection are recorded after each dialysis session by the local investigators in a patient record book (Tabs II. and III).

For each included patient, the mean blood flow has to be calculated at the end of the dialysis session (within the 5 last minutes as the ratio of the blood volume treated/dialysis time in minutes) and to be compared to the baseline TCC function to evaluate the need of urokinase administration.

A fax mentioning the relevant parameters of dialysis (mean blood flow, use of urokinase, TCC-related infection or systemic fibrinolysis) is sent twice per month to the principal investigator to check protocol adherence.

Data are recorded from study entry until study completion (6 months) or until the occurrence of a censuring event (patient’s death, use of AVF, transfer to another HD center, transfer to peritoneal dialysis, kidney transplantation, systemic fibrinolysis or removal of the TCC).
### TABLE III - Study period table

<table>
<thead>
<tr>
<th>Parameter</th>
<th>(Pre)-screening</th>
<th>Optional addit visit</th>
<th>Month 1</th>
<th>Month 2</th>
<th>Month 3</th>
<th>Month 4</th>
<th>Month 5</th>
<th>Month 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>General data</td>
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<tr>
<td>Demographical (age, sex)</td>
<td>X</td>
<td></td>
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<tr>
<td>Verify baseline data</td>
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<tr>
<td>Calculate mean of the average blood flow during the 3 screening dialysis sessions</td>
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<td>X</td>
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<tr>
<td>Verify inclusion/exclusion</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Informed consent</td>
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<tr>
<td>Randomization</td>
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<tr>
<td>Blood volume treated in mL</td>
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<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Dialysis time in min</td>
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<tr>
<td>Mean blood flow (Qb) during dialysis session (blood volume/time on dialysis) in mL/min</td>
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<td>X</td>
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<td>X</td>
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<td>Use of urokinase and reason</td>
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<td>X</td>
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<tr>
<td>Presence of catheter-related bacteremia/exit-site infection</td>
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<tr>
<td>Systemic fibrinolysis therapy</td>
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<td>Removal of the TCC and reason</td>
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<td>Holiday (departure and return date)</td>
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<td>CRP</td>
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<td>X</td>
<td>X</td>
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<td>X</td>
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<td>Monitoring of dialysis efficacy</td>
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<td>URR</td>
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<td>Single pool Kt/V</td>
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<tr>
<td>Administration of study medication</td>
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</table>

TCC = tunneled cuffed catheter; CRP = C-reactive protein; URR = urea reduction ratio.
Patients who decide to be dialyzed in another center during the study will be censored for the period they are not receiving the study medication.

**Statistical analysis**

We arbitrarily considered a 50% reduction of the use of urokinase as clinically relevant. A review of patients with at least 2 therapeutic urokinase treatments over a 6-month period showed that these patients had a median of 3 urokinase treatments over 6 months (range 2-9). We expect a median of 2 urokinase treatments over 6 months (range 1-5) with the Taurolock-HEP500.

Sample size calculation for rank data with ties (14) indicates that, considering a drop-out rate of 20%, with a type I error of 5% and a power equal to 80%, 46 patients in total are needed (23 patients by group) in order to recruit 18 valuable patients by groups in total.

Considering a drop-out rate of 20%, with a type I error of 5% and a power equal to 90%, 64 patients in total are needed (32 patients by group) in order to recruit 25 valuable patients by groups in total.

The primary outcome is expressed as number of catheter dysfunctions requiring urokinase treatment. Hypothesis testing will be done by Wilcoxon rank sum test.

To take into account of differences in time at risk due to catheter removal and patient drop-out in the two arms of the study, the primary outcome will also be expressed as number of catheter dysfunctions requiring urokinase treatment per 100 patient years at risk and will be expressed with 95% confidence intervals. Time at risk for calculation of the incidence rate of catheter dysfunction is defined from inclusion to either end of the 6-month follow up period or the occurrence of a censuring event (TCC removal, treatment of catheter dysfunction with systemic thrombolytic therapy, patient’s death, change of HD center, use of AVF, shift to peritoneal dialysis or kidney transplantation). The effect of the intervention will be expressed by the rate ratio with 95% confidence interval. Hypothesis testing will be done by Poisson regression or eventually by negative binomial regression modeling in case the distribution of outcomes does not follow the Poisson distribution. These regression models also allow hypothesis testing and calculation of rate ratios after adjustment for covariates.

Survival free of the primary endpoint will be calculated by the Kaplan-Meier method with 95% confidence estimates. Hypothesis testing will be done using the log-rank test.

All patients with available data will be analyzed according to the intention-to-treat principle. Time at risk for the development of the outcomes of interest stops at removal of catheter secondary to any cause, treatment of catheter thrombosis with systemic thrombolytic therapy, withdrawal of consent for collection of data, renal transplantation, patient death or loss to follow-up. The effect of the intervention on the primary and secondary outcomes will also be analyzed in an “on therapy” population. Patients in whom the study medication was not administered for more than two consecutive weeks will be excluded from the “on therapy” analysis.

**Conclusion**

This multicenter, randomized, double-blinded and placebo-controlled study is the first trial to assess the efficacy of prophylactic urokinase-containing locking solution in an ideal target population having recurring thrombotic TCC dysfunctions. We consider the study protocol of interest to health-care professionals active in the domain of hemodialysis. Our protocol is adequately powered to detect a clinically meaningful reduction in the incidence rate of thrombotic dysfunction and therefore has the potential to identify a cost-effective and simple strategy to reduce the negative impact of thrombotic TCC dysfunction on hemodialysis adequacy, morbidity and patient’s quality of life.

The protocol raises attention to the persisting need for adequately designed trials addressing important clinical problems in the domain of hemodialysis therapy and dialysis access with TCC in particular.

**Disclosures**

Financial support: None of the investigators has received funding from Tauro-Implant for work realized in the context of the present clinical trial. Tauro-Implant provides the study medication and the corresponding placebo free of charge to the patients participating in the trial. Tauro-Implant does not provide additional funds for the realization of the trial, has not participated in the writing of the study protocol and has no role in the collection of data, as well as analysis, interpretation and presentation of the results.

Conflict of interest: None of the authors has financial interest related to this study to disclose.

**References**
