Research elective

‘The role of urokinase in central venous catheter dysfunction during hemodialysis’

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Summary

Written as an Abstract

**Background and Objectives:** Use of a central venous catheter (CVC) for hemodialysis (HD) is associated with thrombotic complications and dysfunction resulting in a lower adequacy of dialysis. Use of a CVC has higher morbidity and mortality compared to other vascular access options. The primary aim of this study is 1) to evaluate the effectiveness of urokinase when treating dysfunctional CVCs. Secondary aims are 2) to describe patient and dialysis characteristics of patients using a CVC, 3) to identify indications resulting in the use of a semi-permanent CVC and 4) to describe the incidence of dysfunction, CVC-removal and to describe CVC-survival.

**Methods:** This is a retrospective cohort study were data was obtained from the digital patient file. Analysis was performed with data from all patients with a semi-permanent CVC in 2012 and 2013 in Dianet (AMC). Data from 102 patients were used after exclusion. Dysfunction is defined as a blood flow <200 ml/min measured on the dialysis machine. For the statistical analysis of the primary aim, multivariate linear regression models were used.

**Results:** The mean age was 55 years, 49.5% is male and 60% is Caucasian. The total number of dialysis sessions included is 12,906.
1) No significant effect from urokinase on catheter function has been found. In 63.5% of the dysfunctional sessions urokinase was given as a bedside intervention. After urokinase 66.4% of the CVCs were functional during the same dialysis session or at the start of the subsequent dialysis session. However 60.3% of the dysfunctional CVCs became functional without the use of urokinase.
2) In the multivariable analysis associations with the incidence of dysfunction were found for number of CVCs removed during the study period and the incidence of lumen reversal. No other associations between the incidence of dysfunction and patient characteristics were found to be significant.
3) 46% of the patients with a semi-permanent CVC are waiting for fistula or graft placement or maturation. In 19% no other vascular access option is available.
4) The incidence of dysfunctional sessions is 2.16% of the total sessions. Tunneled single lumen CVCs show a slightly better CVC survival compared to tunneled double lumen CVCs. Femoral CVCs show a higher incidence of dysfunction and lower CVC survival compared to internal jugular CVCs.

**Conclusion:** When using urokinase to improve blood flow in dysfunctional central venous catheters the outcomes are uncertain. No significant effect on blood flow improvement of urokinase has been found. No relevant patient characteristics were found to predict the incidence of dysfunction. New prospective research evaluating different interventions could give more definitive results.
Introduction

Aims
A central venous catheter (CVC) is a commonly used vascular access method for hemodialysis (HD) patients. Dysfunction of CVCs is a frequent problem and a reason for under-dialysis. The primary aim of this study is 1) to evaluate the effectiveness of urokinase when treating dysfunctional CVCs. Secondary aims are 2) to describe patient and dialysis characteristics of patients using a CVC, 3) to identify indications resulting in the use of a semi-permanent CVC and 4) to describe the incidence of dysfunction, CVC-removal and to describe CVC-survival.

Goals and hypothesis
This study will investigate the effect of bedside interventions in case of dysfunctional CVCs. The hypothesis is that urokinase locking solution will improve blood flow in dysfunctional CVCs. This is a retrospective cohort study using the existing patient files in 2012 and 2013. The goal of this study is to help nephrologists determine what bedside intervention to use and what the expected results are of these interventions. The secondary aims can contribute to a better understanding of the patient and dialysis characteristics of patients using a semi-permanent CVC for hemodialysis.

Vascular access
Effectiveness of the hemodialysis relies on a vascular access with steady blood flow. The ideal vascular access delivers a stable dialysis blood flow, is long lasting and has little or no complications. The preferred vascular access for HD is the surgically created arterio-venous (AV)-fistula followed by the AV-graft. The AV-fistula has the lowest complication rates and best 5-year survival. A central venous catheter (CVC) can be used in the acute setting, as a bridge therapy towards other vascular access options or when a graft or fistula is not possible. Despite national and international guidelines CVCs are frequently used as a semi-permanent vascular access and this portion has increased in recent years. The main disadvantages of a CVC are the risk of infection, the frequent dysfunctional sessions and flow problems due to thrombotic complications. There is also a risk of central venous stenosis, especially when using the subclavian veins. This study will focus primarily on the noninfectious catheter-related dysfunction.

Central venous catheter
The use of a CVC is associated with higher morbidity, mortality, more invasive interventions and more hospital admissions compared to the AV-fistula. The current guidelines in Europe and the United States discourage the use of a CVC. Despite these guidelines and recommendations over 17% of the semi-permanent vascular access for hemodialysis is a CVC in the United States. In Europe the numbers are diverse, ranging from 3% in Germany to 23% in the United Kingdom.
Most CVCs are used in the acute setting for a limited time. Prolonged use of a CVC is associated with relatively higher risks of thrombotic and infectious complications. This study will focus on the semi-permanent use of a CVC. Indications for a CVC are shown in figure 1.

![Diagram showing indications for the use of a CVC for HD. This study has excluded the 'acute setting'.](image)

Especially for older patients the use of a CVC has shown higher mortality rates due to CVC complications compared to younger patients.\(^\text{12}\)

The preferred location of a CVC for the semi-permanent use is the right internal jugular vein because of the anatomy that allows easy access to the right atrium. The right jugular vein is associated with lower risk of dysfunction and more stable blood flows compared to the femoral and subclavian veins.\(^\text{13}\) The left internal jugular vein is a good alternative with similar morbidity and mortality. Other options like the femoral or subclavian veins show more complications like central venous stenosis and dysfunctional dialysis sessions.\(^\text{14}\)

Several kinds of CVCs are used for hemodialysis. A CVC can have a single or double lumen and they can be tunneled, untunneled or straight untunneled. In the Netherlands the most common used for semi-permanent access is the tunneled double lumen catheter.\(^\text{15}\) The evidence for the choice between single and double lumen or tunneled and untunneled CVCs is limited and does not show consistent outcomes.\(^\text{14-17}\) Temporary untunneled CVCs are associated with more complications compared to tunneled CVCs.\(^\text{18}\)

Newer design of the tunneled double lumen catheters include an identical peripheral tip for both lumens, which may reduce the amount of recirculation when dealing with dysfunction. Literature shows little or no difference in performance comparing the different designs and brands.\(^\text{14,19}\)
CVC dysfunction and complications

The most dangerous complication of a CVC is bacteremia and sepsis. With a semi-permanent CVC in situ the chance of bacteremia is 27.5% in 1 year. Sepsis occurs with an incidence of 1.3/1000 catheter days. 20 Secondly there are dysfunctional CVCs leading to low blood flows and inability to supply adequate HD. Dysfunctional CVCs are a frequent issue with chronic hemodialysis patients. 17 Between 20-30% of CVCs have dysfunctions after 120 days. 21 The overall survival rate and incidence of dysfunction differs between multiple studies. 22,23 A large study with the tunneled single lumen Tesio ® CVC shows a 1-year survival rate of 74% and a 2-year survival rate of 44%. 24 Thrombotic and infectious complications occur with an incidence ranging between 0.254 – 5.5/1000 catheter days. 9,21,25,26 Dysfunctional dialysis sessions occur in a similar study around 6-7/1000 HD sessions. 27 Most studies show no associations between patient or dialysis characteristics and the risk of dysfunction. 14,16 Only one small study shows patient factors like diabetes and the number of previous CVCs increase the risk of dysfunction. 17

The effects of dysfunction and other complications are based the increased morbidity and mortality, increased health care costs and a lower quality of life perceived by the hemodialysis patients. Over 60% of the patients with a CVC suffers from anxiety concerning the vascular access for hemodialysis. 28

Dysfunction is defined in Europe as a blood flow <200 ml/min or a pre-pump arterial pressure <-250 mmHg. The definition of dysfunction in the United States differs because of the different dialysis methods with higher flows and pressures compared to common practice in Europe. 3

Literature describes early and late dysfunction. 14 Early dysfunction occurs shortly after the CVC placement, mostly due to mechanical problems like incorrect tip placement, damage to the lumen, kinking of the CVC after placement or flow obstruction when the CVC tip lies against the vessel wall. Late dysfunction occurs mostly due to progressive occlusion by fibrin sheaths or the forming of a thrombus.

Types of thrombotic occlusions are shown in figure 2. The thrombus may be located inside the lumen or at the tip of the CVC or it may be located outside the lumen causing compression and thus dysfunction. Lastly a fibrin sheath may form with connective tissue causing a web of fibrin. Dysfunction is mostly due to thrombotic complications, however research on this subject is limited. 14 The forming of a fibrin sheath was first described in an in-vivo study where a silicon catheter was placed in rats. 29

The Virchow triad can be used to describe the pathophysiology of this thrombus forming. First there is endothelial injury due to the insertion of the CVC. Second there are hemodynamic changes like stasis during the interdialytic period and turbulence due to the
CVC tip disrupting normal blood flow. Third literature describes a hypercoagulability state due to CVC insertion. 30

Signs of CVC dysfunction include not being able to aspirate blood freely, low blood flow, increased arterial pressure and frequent pressure alarms not responsive to patient repositioning or catheter flushing. 4 The dialysis nurse plays a central role in the detection and early treatment of CVC dysfunction. 31

Recirculation and reversal of lumens
A common problem with catheter dysfunction is the recirculation. Recirculation occurs when dialyzed blood mixes with undialyzed blood thus lowering the adequacy and efficiency of the dialysis session. Especially when reversing the lumens the recirculation can become as high as >20%. Reversal of lumens of a CVC means connecting the arterial connection of the dialysis machine to the venous connection of the CVC and the other way around. This results in an Art-Ven, Ven-Art connection and thus reversing the normal blood flow inside the lumen(s) of the catheter compared to the normal connection Art-Art, Ven-Ven. When dealing with thrombotic complications this reversal can help to improve blood flow for a limited amount of dialysis sessions. 14 Literature shows high rates of recirculation occur mostly in femoral catheters with an additional increased effect when reversing the lumens compared to jugular CVCs, probably due to the longer lumens of femoral CVCs. 32 Reversal of jugular CVCs show an increase of recirculation from 2 to 10%. 2 The consequences of higher recirculation and possible lower adequacy have not been clearly stated in the literature. When dealing with dysfunctional CVCs, reversal of lumens might improve adequacy of HD despite the higher recirculation rates. Studies have shown increased urea clearance in reversed dysfunctional CVCs compared to unreversed dysfunctional CVCs. 33

Prevention and interventions
Recent reviews in 2012 and 2013 make recommendations for the prevention and management of CVC dysfunction and thrombotic complications. 14 These interventions can be divided in bed-side interventions and invasive interventions. The invasive interventions consist of replacing the current CVC using the in situ guide wire or placing a new CVC. Replacement of the CVC is relatively expensive, invasive, time-consuming and has an increased risk of complications. 14 Therefore it is seen as a last resort in catheter dysfunction. This study will focus on the bed-site interventions, which are listed below.

1. Changing the position of the patient during dialysis
2. Flushing of both lumen during dialysis with NaCl
3. Reversal of lumens (arterial-venous and venous-arterial)
4. Locking solutions with urokinase, discussed below

Other, more invasive, interventions like stripping the lumen or intra-luminal brushing seem to have a possible effect on improving blood flow in case of CVC dysfunction. However there are concerns about showering micro-organisms in the circulation and possible arrhythmias. Moreover the stripping has a high technical success rate but this is short lived when looking at CVC survival. 14,34 Systemic therapy with Aspirin®, Warfarin® or Acenocoumarol® show no positive effect on the incidence of dysfunctions. 4
**Interdialytic locking solutions**

Locking solutions are solutions of anti-microbial and thrombolytic agents that can help to prevent infectious and prevent or treat thrombotic complications like dysfunctional CVCs. The lumen is filled with 1.5 – 2.2 ml of locking solution for 30-60 minutes or left in place in between dialysis sessions (interdialytic period). Commonly used locking solutions are citrate, heparin and plasminogen activators like urokinase. The pathophysiology is that ‘locking’ the CVC with an anticoagulant will prevent and possibly treat catheter related thrombosis and extend CVC survival. Heparin has shown systemic anticoagulation complications, like heparin-induced thrombocytopenia, especially when using higher doses >1000 units/ml. Because of these possible inadvertent and the anti-microbial effect, Citrate is favored above Heparin, showing similar thrombosis and dysfunction rates and possible higher cost-effectiveness.

Most relevant studies have been investigating the prophylactic effect of Citrate versus Heparin locks. The few studies investigating plasminogen activators (PA) show an advance of PA compared to heparin with better flows and fewer complications. However these were all small uncontrolled studies. These studies use blood flow as the main parameter of CVC dysfunction.

Research investigating the effect of these thrombolytics, like urokinase, when trying to improve blood flow in dysfunctional CVCs is limited and don’t have consistent outcomes. 50-90% of the CVCs have better flows after the use of a thrombolytic locking solutions. Recent studies suggest thrombolytics can be used to prevent CVC dysfunction in vulnerable patient groups. However the mean gain of CVC survival is 14 days or 5-7 dialysis sessions. In a recent study investigating Tenecteplase, 34% of the dysfunctional CVCs were functional after a 1 hour dwell in Tenecteplase. In the extended dwell group 49% was successful.

One possible problem with interdialytic locking solutions might be the leakage of anticoagulant into the systemic circulation because of the parabolic flow in the CVC. Blood will replace the leaked anticoagulant and thrombosis might be accelerated, especially in between dialysis sessions.

**Dianet AMC**

The dialysis department of Dianet (AMC) has 130 chronic HD patients. A relatively large portion of the dialysis population uses a CVC as a semi-permanent vascular access for HD. By investigating patient characteristics of this patient group and the interventions when dealing with dysfunctional CVCs, protocolling might improve and more evidence based interventions may be used.
Methods

Study design and patients
This is a retrospective cohort study using the digital patient files. This study included all patients on hemodialysis with a semi-permanent central venous catheter in Dianet (AMC) who received hemodialysis in 2012 and/or 2013. A list of patients was acquired via the financial database and treatment codes. Only chronic hemodialysis patients were included. Patients who received hemodialysis via a CVC in the acute setting were excluded. The definition of acute dialysis is intermittent hemodialysis <1 month. Only patients older than 18 years were eligible for enrollment.

Because of the retrospective design no ethics review board approval was acquired.

Data collection

Demographic data: Clinical and demographic data were collected through review of the digital patient dialysis database Diamant®. Age was calculated using the 1st of January 2012. Ethnicity was subtracted from the medical file in Diamant® or by using the patient’s picture of the AMC patient file. When no picture or place of birth were found they were defined as ‘other/unknown’. The number of dialysis sessions was calculated between the start-and end-date together with the prescribed number of dialysis per week.

Primary outcome (1): The primary outcome of this study is the effect of the urokinase locking solution when dealing with catheter dysfunction. Dysfunction is defined as an inability to maintain a blood flow <200 ml/min, despite flushing and positional changes of the patient. This blood flow was extracted from the nurse report. The blood flow is not an actual measurement but it is adjusted by the dialysis nurse. The dialysis nurse will adjust the blood flow when either 1) No blood flow is possible 2) Arterial pressure is becoming <250mmHg or 3) frequent alarms not responsive to patient repositioning or catheter flushing.

Urokinase is administered as a 30-90 minute dwell when the patient is inside the dialysis center or as an interdialytic locking solution. The indication for administering urokinase is made by the dialysis nurse or the nephrologist.

A positive effect from the urokinase is defined as an increase of blood flow ≥ 200 ml/min. No effect was defined as a blood flow remaining <200 ml/min, thus the CVC remains dysfunctional. The effect could be in the same dialysis session, defined as an ‘early effect’ or at the start of the next dialysis session, defined as a ‘late effect’.

As intervention urokinase locking solution with a concentration of 5000-25000 U/lumen was used filling the lumen with 1.5-2.2 mL, depending on the brand of CVC and manufacturers prescription.

This locking solution can be used either as a 30 or 60 minute dwell during the dialysis session or for a number of days in the interdialytic period.
Secondary outcomes (2-4):
Duration of the indication for a CVC was calculated between the start date of hemodialysis via a CVC and the end date when the indication was no longer applicable. The following grouping method was used for indications.
1. Short life expectancy
2. Waiting for AV-fistula/graft surgery or maturation
3. Waiting for a renal transplant
4. Waiting for peritoneal dialysis catheter placement
5. Shunt surgery is not possible or previous shunts have failed
6. Patient refusal
The nurse report of every dialysis sessions was analyzed for the words related to re-pooling.

The duration of a matured shunt and a CVC in situ at the same time was calculated using the first date a matured shunt has been used and the removal date of the CVC.
The indication for the different kind of CVCs like tunneled or untunneled is made by the nephrologist. CVC survival is calculated for CVCs removed because of infection, dysfunction or dislocation. CVCs are placed by either the nephrologist or the vascular surgeon in this center.

Literature research
For the literature research PubMed was searched for articles in English. The following search items were used, "central venous catheters"[MeSH] OR "catheters" AND ("haemodialysis"[MesH] OR "renal dialysis"[MeSH] AND "complications" OR "dysfunction"). Secondly the following terms were used searching for the effect of urokinase or other locking solutions: "locking solution" OR "urokinase" OR "heparin" OR "citrate" AND "haemodialysis"[MESH]. Lastly the reference section of relevant studies was searched for additional studies.

Data analysis
To evaluate the effect of urokinase on the dysfunction a linear regression model was used. Because multiple dysfunctions can occur within one CVC, and multiple CVCs can be included from one patient, the results were corrected for the multiple levels. These levels are shown in figure 4. A multi-level regression model was used to correct for the effect of the multi-level design of the data. In SPSS the Generalized Linear Mixed Model (GLMM) was performed.

![Fig 3. Visualization of different levels when analyzing dysfunctions.](image-url)
Statistical analysis

The data are presented as means with standard deviation (SD) or medians with interquartile ranges (IQR). Results were considered statistically significant when a two-sided p-value of ≤0.05 was achieved.

The average percentage of missing values per variable was 2%. Most data were not normally distributed. To identify possible confounding factors to the incidence of dysfunction the Mann Whitney tests and Chi-Square tests in SPSS were used. A Mann Whitney test was used to compare CVC survival between the different locations of the CVC and between the type of CVC. A linear regression analysis was used to study the relation between each variable on dysfunction and CVC-survival. Because of the multi-level design of this study a Generalized Linear Mixed Model has been used to adjust for the effect of the patient-and CVC-level on the individual cases.

All calculations were made by use of the 64-bit statistical package (SPSS for Windows Version 20; SPSS Inc. Headquarters, Chicago, Illinois, US).
Results

Baseline: Patients

A total of 102 patients were included for analysis. The baseline characteristics of the total cohort is listed in table 1. The mean age was 55 years (±17). Of the 102 patients 50% were male. 59% of the patients were Caucasian, 30% Negroid and 6% Asian. Primary renal disease 27% were vascular origin, 22% diabetic and 17% systemic. Medical history shows 77% of the patients have confirmed hypertension and 37% have diabetes. 53% of the patients use systemic anticoagulant therapy, like vitamin K antagonists and thrombocytes aggregation inhibitors like Aspirin®. Dialysis history shows patients have a history of median 390 days (IQR 0-3202) of renal replacement therapy before the start of this study. 50% of the patients had an average of 2 CVC before this study.

| Table 1. Baseline characteristics of the patient group receiving HD via a semi-permanent CVC. |
|---|---|---|---|
| Characteristic | n or median | % or SD/IQR |
| Number of dialysis sessions in 2012 and/or 2013 included | 12.709 sessions |
| Number of patients included | 102 patients |
| Demographic and social | | |
| Age group, mean (yrs.) | 55 years ±17.3 yrs |
| .1-30, n (%) | n13 12.6% |
| .31-45, n (%) | n20 19.4% |
| .46-65, n (%) | n34 33.0% |
| .>65, n (%) | n34 33.0% |
| Gender male % | 50 49.5% |
| Race | | |
| .Caucasian, n (%) | n60 59.4% |
| .Negroid, n (%) | n32 31.7% |
| .Asian, n (%) | n6 5.9% |
| .Other / unknown, n (%) | n3 3.0% |
| Primary renal disease | | |
| Vascular, n (%) | n27 26.7% |
| Diabetic nephropathy, n (%) | n22 21.8% |
| Systemic disease / nephritis, n (%) | n17 16.8% |
| Cystic disease, n (%) | n6 5.9% |
| Other, n (%) | n29 28.7% |
| Medical history | | |
| Diabetes, n (%) | n37 36.6% |
| Hypertension, n (%) | n78 77.2% |
| Myocardial infarction, n (%) | n22 21.8% |
| Vascular disease, n (%) | n24 23.8% |
| Cerebral vascular incident, n (%) | n17 16.8% |
| Systemic use of anti-coagulants | | |
| .No anti-coagulants | n48 47.5% |
| .Thrombocytes aggregation inhibitors | n28 27.7% |
| .Vitamin K antagonists | n25 24.8% |
| Dialysis history | | |
| Total duration of renal replacement therapy | 390 days IQR 0-3202 |
| Total duration of (semi-)permanent CVC | 27 days IQR 0-1061 |
| CVC in history, n (%) | n50 50% |
| .Average number of CVC in history | 2 CVCs IQR 0-4 |
| Average number of fistula’s/grafts in history | 1 shunt IQR 0-1 |
Aim 1: Effect of urokinase

Figure 1 shows the number of dysfunctions, interventions and effects of these interventions. A total of 274 dysfunctional dialysis sessions occurred during the study period. In 64% of these dysfunctional sessions urokinase is given (A), in 7% a new CVC is placed (B) and in 29% no urokinase has been given (C).

A. When urokinase is given, in 64% the catheter function is restored, 45% in the same dialysis session and 55% in the subsequent dialysis session. In 36% of the cases the catheter remains dysfunctional with a flow <200 ml/min.
B. In 7% a new CVC is placed without urokinase. All replaced CVCs were functional directly after (re)placement.
C. When no urokinase is given, in 60% the catheter function is restored in the next dialysis session. In 40% the catheter remains dysfunctional.

Effect urokinase on dysfunction: regression analysis and GLMM

A total of 274 dysfunctions in 119 different CVCs in 51 different patients are included. In the multi-level linear regression model no significant effect from the urokinase has been found.
**Aim 2: Patient and dialysis characteristics**

Results of patient and dialysis history are shown in the baseline table 1. When looking for confounding factors to the incidence of dysfunction, two groups were formed by using the relative portion of dysfunctional dialysis sessions. Group 1 (n70) has patients with 0-5% of dysfunctional dialysis sessions. Group 2 (n31) has >5% dysfunctional dialysis sessions. Table 2 shows the associations between the two groups. The total number of CVCs and the total number of CVCs removed within the study period is significantly higher in group 2 (P <0.01). Furthermore the incidence of reversal of lumens is significantly higher in group 2 (P<0.01).

Other variables such as the number of previous CVCs and patient history like Diabetes were not associated with the risk of dysfunction (P>0.05). No other significant factors were associated with the incidence of dysfunction have been identified.

Table 2. Mann Whitney and Chi-Square test to compare means group 1: less 5% dysfunction and group 2: >5% dysfunction

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1: low incidence n71</th>
<th>Group 2: high incidence n31</th>
<th>Sig. between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seks</td>
<td>51% male</td>
<td>45% male</td>
<td>0.133</td>
</tr>
<tr>
<td>Age</td>
<td>54 yrs (±18)</td>
<td>54 yrs (±16)</td>
<td>0.590</td>
</tr>
<tr>
<td>Systemic anti-coagulant therapy</td>
<td>49% no therapy</td>
<td>45% no therapy</td>
<td>0.175</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>36%</td>
<td>39%</td>
<td>0.751</td>
</tr>
<tr>
<td>Primary diagnosis</td>
<td>23% vascular</td>
<td>29% vascular</td>
<td>0.641</td>
</tr>
<tr>
<td></td>
<td>16 interstitial</td>
<td>19 interstitial</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30% other</td>
<td>26% other</td>
<td></td>
</tr>
<tr>
<td>Number of CVCs in history</td>
<td>2 (IQR 0-4)</td>
<td>2 (IQR 0-3)</td>
<td>0.691</td>
</tr>
<tr>
<td></td>
<td>471 (IQR 0-2775)</td>
<td>379 (IQR 0-3534)</td>
<td></td>
</tr>
<tr>
<td>Total length of renal replacement therapy in history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% reversal of lumens</td>
<td>6% (IQR 0-10)</td>
<td>16% (IQR 6-22)</td>
<td>0.001*</td>
</tr>
<tr>
<td>No CVCs included in this study</td>
<td>1 (IQR 1-2)</td>
<td>2 (IQR 1-4)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>No CVCs removed in this study</td>
<td>1,27 (±1,03)</td>
<td>2,61 (±2,28)</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

**Aim 3: Indications for a CVC**

In figure 5 indications for the CVC are listed. Patients who are waiting for shunt placement have a CVC for a median length of 159 days (IQR 88-248). The minimum waiting time for a shunt is 20 days, the maximum 1491 days. Patients waiting for renal transplantation use a CVC for a median of 189 days (IQR 131-726). Patients were no shunt is possible have a CVC for a median of 1506 days (IQR 508-2274).
Mature shunt
When a fistula or graft is matured the CVC is left in place for a median of 40 days (IQR 12-68). This means in the group ‘Waiting for shunt placement’ that patients who have a matured shunt and it has been proven to be functional, the existing CVC is left in place for a number of weeks.

Aim 4: CVC dysfunction and survival
56 patients had one or more dysfunctional dialysis sessions. The total number of dysfunctional dialysis sessions is 274, leading to an incidence of dysfunction of 2.16%.

CVC characteristics
Types, brands and locations of CVCs used are listed in table 3. 12 Different brands of CVC were used in this center in 2012 and 2013. The most frequently used brands are the Palindrome (28%), Kimal (13%) and Tesio (10%). 29% of the CVCs is a double lumen tunneled catheter, 24% an untunneled double lumen and 10% a tunneled single lumen catheter. The majority of CVC are placed in the right and left internal jugular vein (39% and 14% respectively), 14% was placed in the right or left femoral vein.
Table 3. Central venous catheter (CVC) characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type CVC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tunneled double lumen</td>
<td>93</td>
<td>42.7</td>
</tr>
<tr>
<td>Untunneled double lumen</td>
<td>76</td>
<td>34.9</td>
</tr>
<tr>
<td>Tunneled single lumen</td>
<td>32</td>
<td>14.7</td>
</tr>
<tr>
<td>Other</td>
<td>16</td>
<td>7.3</td>
</tr>
<tr>
<td><strong>Brand CVC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palindrome</td>
<td>88</td>
<td>40.4</td>
</tr>
<tr>
<td>Kimal</td>
<td>41</td>
<td>18.8</td>
</tr>
<tr>
<td>Tesio</td>
<td>32</td>
<td>32.0</td>
</tr>
<tr>
<td>Joline</td>
<td>8</td>
<td>3.7</td>
</tr>
<tr>
<td>Gamcath</td>
<td>14</td>
<td>6.4</td>
</tr>
<tr>
<td>Jet</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Ash split</td>
<td>5</td>
<td>2.3</td>
</tr>
<tr>
<td>Medcomp</td>
<td>12</td>
<td>5.5</td>
</tr>
<tr>
<td>Other / unknown</td>
<td>16</td>
<td>7.3</td>
</tr>
<tr>
<td><strong>Location of CVC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right internal jugular vein</td>
<td>122</td>
<td>56.0</td>
</tr>
<tr>
<td>Left internal jugular vein</td>
<td>45</td>
<td>20.6</td>
</tr>
<tr>
<td>Left or right femoral vein</td>
<td>43</td>
<td>19.7</td>
</tr>
<tr>
<td>Left or right subclavian vein</td>
<td>5</td>
<td>2.3</td>
</tr>
<tr>
<td>Other / unknown</td>
<td>3</td>
<td>1.4</td>
</tr>
</tbody>
</table>

CVC survival
Results for CVC survival are listed in table 5. The survival of a CVC varies between 3 till 3234 days. Median survival is 117 days (IQR 36-253). Median survival in the tunneled double lumen group was 168 days (IQR 69-282) and thereby significantly shorter (P<0.001) compared to the median survival in the tunneled single lumen group of 256 days (IQR 68-933). Median survival in the right jugular vein is 152 (IQR 47-263), while median survival in the femoral veins is 32 (IQR 10-72), significantly different with P<0.001. Kaplan-Meier curves show the difference in CVC survival in figure 6 and 7.
Table 4. CVC survival

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>median survival</th>
<th>IQR</th>
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<tbody>
<tr>
<td>CVC survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimum - maximum</td>
<td>3-3234 days</td>
<td></td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>260 ± 446</td>
<td></td>
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<tr>
<td>Type CVC</td>
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<tr>
<td>Tunneled double lumen</td>
<td>168</td>
<td>69-282</td>
</tr>
<tr>
<td>Untunneled double lumen</td>
<td>45</td>
<td>17-118</td>
</tr>
<tr>
<td>Tunneled single lumen</td>
<td>256</td>
<td>68-933</td>
</tr>
<tr>
<td>Other</td>
<td>31</td>
<td>11-188</td>
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<tr>
<td>Location of CVC</td>
<td></td>
<td></td>
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<tr>
<td>Right internal jugular vein</td>
<td>152</td>
<td>47-263</td>
</tr>
<tr>
<td>Left internal jugular vein</td>
<td>176</td>
<td>54-562</td>
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<tr>
<td>Left or right femoral vein</td>
<td>32</td>
<td>10-72</td>
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<td>Left or right subclavian vein</td>
<td>228</td>
<td>151-358</td>
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<tr>
<td>Other / unknown</td>
<td>36</td>
<td>36-133</td>
</tr>
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</table>

CVC removal

184 of the total of 218 CVCs were removed during the time period of this study. Reasons for CVC removal are listed in figure 8. The main reason for CVC removal is catheter dysfunction (21%), followed by a matured shunt (17%), protocol (12%) or infection (8%). 6% of tunneled, cuffed catheters were removed because of dislocation (6%), for example when the tunneled CVC stitching failed or when patients accidently pulled the CVC out.
Discussion

Summary results (aims)
1. This retrospective study suggests that urokinase gives no statistically significant improvement of the blood flow when dealing with catheter dysfunction.
2. Patient and dialysis characteristics show no relevant associations to the incidence of dysfunction.
3. The most common indication for semi-permanent use of a CVC is waiting for fistula or graft surgery or maturation followed by the impossibility for creation of a graft of fistula. When a fistula or graft is matured the CVC is left in place for a median of 40 days.
4. The incidence of CVC dysfunction is 22/1000 dialysis sessions. Furthermore the results show a slight advance of tunneled single lumen catheters in CVC survival compared to the tunneled double lumen CVCs.

Aim 1: Effect of urokinase
Current literature shows thrombolytics are commonly used to help dissolve thrombotic occlusions causing catheter dysfunction. However studies investigating the effectiveness of urokinase don’t have consistent outcomes. Our results show that 60% of the dysfunctional CVCs have better flows when urokinase is given, compared to other studies ranging between 50-90%. However the regression analysis shows no significant effect from urokinase. Despite the use of new designs of CVCs, urokinase and other locking solutions most CVCs still become dysfunctional. Much of the etiology of dysfunctional CVCs is still not clearly understood. One possible explanation for the failing of urokinase to treat dysfunctional CVCs is that there might be no thrombotic etiology in a portion of the dysfunctional CVCs. For example a malposition of the CVC-tip against the vessel wall might play a role when dealing with dysfunctional CVCs.

Implications for daily practice
When dealing with CVC dysfunction the bedside interventions are the main treatment for prolonging CVC survival. After these interventions only a CVC replacement is the last resort for improving the blood flow and therefore the dialysis adequacy. This study shows no significant effect from urokinase, however this study has several limitations that will be discussed later. For the clinician this study might help to judge the effect of urokinase when considering it as a treatment. However since it is one of the last interventions before CVC removal, urokinase will probably still be given despite its moderate effect. The possible positive effect on the blood flow and avoiding high complication rates due to CVC replacement make it a preferably intervention.
Aim 2: Patient and dialysis characteristics
Compared to other studies similar primary renal disease and medical history are found in this study. However to adequately compare the group using a semi-permanent CVC with the fistula, graft or PD group, these groups should be investigated in the same manner in the same center.
When looking for confounding factors to the incidence of dysfunction, no relevant factors were found. This is in line with most of the available literature. This study has a relatively large study population and number of CVCs compared to existing literature. However the study population of this and other studies remains low, making it difficult to draw conclusions and compare means between samples within the population.

Implications for daily practice
For clinicians it might be helpful to predict higher incidence of dysfunction in certain patient groups. This study shows no patient of dialysis characteristics that can help clinicians. Only the number of CVCs removed during a study period is a significant confounder. Therefore this study shows dysfunction is not easily predictable when looking at patient and dialysis characteristics.

Aim 3: Indications for a CVC
Only 20% of the patients have a semi-permanent CVC because another vascular access method is not possible. Most patients with a semi-permanent CVC are waiting for fistula or graft placement or maturation (45.5%). There are several possible reasons for this relatively large group. First there is a waiting list for fistula or graft surgery, second the operation can be cancelled due to patient specific reasons like a bad overall condition of the patient. Third when a patient has a functioning and matured fistula or graft the CVC is left in place for a mean of 55 days. A possible explanation is that the clinician prefers to have an escape option when the shunt cannot be used. However to have a good view on the reason for this relatively large group the reasons should be investigated separately.
12% of the patients have a semi-permanent CVC because they refuse a fistula, graft or PD. A possible explanation might be that patient with a good functioning CVC don’t want to go through the process of surgery, shunt maturation and punctures.

Implications for daily practice
Important implications for the clinicians are to reduce waiting lists for fistula or graft surgery to minimize morbidity and mortality due to CVC complications. Clinicians should remove a CVC when a fistula or graft is functional and matured. Unnecessary prolongation of the CVC in situ leads to possible complications of the CVC like infection or thrombosis. Furthermore patient education might help to reduce the number of patient refusals to switch to other, more safer, vascular access options.
**Aim 4: CVC dysfunction and survival**

The incidence of CVC dysfunction is 2.16% of all dialysis sessions included, which is comparable with existing literature. When comparing the group with high number of dysfunction, >5% of dialysis sessions, and the group with low number of dysfunction, 0-5% dysfunctional dialysis sessions no significant difference in patient characteristics and patient history has been found. Thus no patient factors can help to predict possible CVC dysfunction. When looking at CVC survival the mean survival is 260 days. This is comparable with existing literature, however literature shows a great variation in CVC survival. The single lumen tunneled catheter has a longer survival compared to the double lumen tunneled catheter. A possible explanation might be the single lumen catheter has less thrombus forming due to the different flow directions. Similar studies focused on comparing single versus double lumen CVCs show no clear advantage. The setup of this study with no randomization, no clear indication to which CVC type a patient will receive and a limited amount of follow-up make these results difficult to interpret for daily practice. Lastly one major disadvantage of a single lumen CVC is that it can only handle relatively low blood flows compared to the double lumen CVCs, leading to possible under dialysis or prolonged dialysis time.

The location of a CVC is preferably the right or left jugular vein. Together with existing evidence this study shows a higher number of dysfunctional sessions when using a femoral vein access.

The main indications for removing a CVC are as expected, dysfunction, infection or another available vascular access. 6% is removed due dislocation of the CVC. This might be avoidable when a CVC is properly glued or stitched and monitored during each dialysis session.

**Implications for daily practice**

CVC survival shows a great variance. For the clinician it is difficult to predict survival for an individual patient. However the femoral access has shown disadvantages in incidence of dysfunction and lower survival rates. When it is possible the femoral vascular access should be avoided. The decision for a single versus double lumen or tunneled versus untunneled CVC should be based on existing literature, doctor- and center-experience. Dislocation of a CVC might be avoided by adequately monitoring signs of dislocation and proper stitching or gluing.

**Overall strengths and limitations**

This study had several limitations.

- This is a single center study with a population that differs from the general Dutch population. The AMC hospital has more Afro-American patients compared to similar dialysis centers in the Netherlands.
- Furthermore the retrospective cohort design and the time period of 2 years resulted in the use of different protocols, doctors and nurses leading to a non-uniform reporting in the patient files. This non-uniform reporting might have resulted in a possible under-reporting of catheter dysfunction and missing data, especially missing blood flow measurements.
Besides this the variation between doctors whether to use urokinase or not has not been uniformly protocolled in this center during the study period. This might have resulted in different decisions and a doctor-bias whether to use urokinase or not.

The lack of a uniform protocol resulted in a variety of uses of the urokinase locking solution. Some locking solutions were left in place for 20 minutes, while others were left in the catheter for 120 minutes or for several days during the interdialytic period.

- Decisions and indications for deciding which type of CVC to use, for example a tunneled versus an untunneled CVC are not clearly protocolled.
- The effect of other minor-invasive bed-side interventions like reversal of lumens and CVC flushing cannot be investigated in this study. Because of the lack of uniform reporting and the frequent reversal and flushing the effect of these minor interventions cannot be determined. Therefore the measured effect of urokinase might be affected by these other interventions.
- The use of blood flow as the main dysfunction and effect parameter has disadvantages. The blood flow is regulated by the nurses input in the dialysis machine based on the number of alarms and desired filtration rate. The use of the blood flow as an effect therefore depends on the dialysis nurses input in the machine. Besides this, no other parameters of dialysis effectiveness were obtained in this study. However the blood flow is the most frequent used parameter in existing literature for catheter function and therefore dysfunction. Furthermore the definition of a blood flow lower than 200 ml/min is commonly used as an indicator for a non-effective dialysis session or dysfunction in national and international guidelines.
- In July 2013 the dialysis center switched from Citralock® locking solution to Taurolock® locking solution, however no significant difference in incidence of dysfunction has been found between 2012 and 2013.

**Prospective**
The perfect locking solution to prevent or dissolve thrombotic complications in CVCs has yet to be found. This study, together with other literature, show varying results on catheter function when using urokinase. However this and other studies have many limitations. The retrospective design of this study and low number of patients make it difficult to interpret the results.

New studies should be prospective in nature and use a clear study treatment protocol to address the limitations resulting from this study. A multi-center study should be undertaken to limit bias per center or doctor. Ultimately a randomized controlled trial comparing the different locking solutions can help the practitioner making an evidence based decision. This and future research can help to make uniform and clear treatment protocols for preventing and treating thrombotic complications in CVCs. Together with the signal function from the dialysis nurse these future protocoling can help to maintain a reliable vascular access for hemodialysis patients.
Conclusion

Aim 1) No significant improvement on blood flow has been found using urokinase. However the retrospective cohort design of this study and lack of uniform protocolling during the study period make it difficult to interpret the results.

Aim 2) No patient or dialysis characteristics have been found to significantly associated to the incidence of CVC dysfunction. This makes assessing the risk of dysfunction difficult to assess.

Aim 3) Most patients with a semi-permanent CVC are waiting for fistula or graft surgery or maturation, with a median waiting time of 152 days. It is important waiting lists and delays in fistula or graft placement must be kept to a minimum to reduce serious morbidity and mortality due to CVC complications. Furthermore patient education from the nephrologist and dialysis nurse is important in reducing the number of patient refusing a fistula, graft or PD. Lastly it is important clinicians remove the existing CVC after the fistula or graft has been matured. By not removing the CVC prolongation of the infectious and thrombotic risks increase patient morbidity and mortality.

Aim 4) The total incidence of CVC dysfunction is 22/1000 dialysis sessions. Single lumen tunneled CVCs show a slight advance in CVC survival compared to double lumen tunneled CVCs. Femoral CVCs show a clear disadvantage in CVC survival and incidence of dysfunction and thus should be avoided when possible.

New research should be prospective in nature with clear protocolling. Ultimately randomized controlled trials to compare different bed-side interventions and the different locking solutions should give more definitive answers. This and future research can lead to clear, evidence-based protocols for preventing and treating dysfunctional CVCs and thereby ensuring a reliable, sustainable vascular access for hemodialysis patients.
Ongoing (prospective) research

Together with my local clinical tutor, Dr. N.C. van der Weerd, I will continue on this subject and we are planning to work on publications resulting from this study. Baseline data from groups of patients using a fistula or a graft during the same study period will be added to the database.

Besides this retrospective study we are working on a prospective study that is already taking place in Dianet Utrecht and Dianet Amsterdam. With this prospective study some of the limitations of this study are addressed. In this new study we are investigating the effect of multiple (minor) interventions when dealing with dysfunctional CVCs, like reversal of lumens, flushing with NaCl and urokinase locking solution. A clear study protocol for the dialysis nurse and a clear treatment protocol for the nurses and nephrologist has been issued and explained. From June 2014 data has been collected for this prospective study. Results are expected to be available by the end of 2014.
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Literature