OPTIMIZING THE MANAGEMENT OF HEMODIALYSIS CATHETER OCCLUSION

BY

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THIS WORK IS DEDICATED TO…

MY PARENTS

Abstract

Background: Hemodialysis catheter occlusion compromises hemodialysis adequacy and increases the cost of care. Repeated administration of alteplase in hemodialysis catheters typically produces only short-term benefits. A step-by-step algorithm describing when and how to administer alteplase, with an emphasis on earlier catheter replacement in specific cases, may reduce the frequency of alteplase administration. The purpose of this study was to design, implement and evaluate the efficacy of an algorithm to optimize the management of hemodialysis catheter occlusion.

Methods: The study had a prospective quasi-experimental design in two parts. Baseline data on the use of alteplase and catheter exchange were collected during Part I; while, Part II consisted of algorithm implementation with collection of similar data. Rates of alteplase use and catheter exchange per 1000 catheter days were the primary and secondary outcomes of the study, respectively.

Results: One-hundred and seventy-two catheters in 131 patients were followed up during the course of the study. The vast majority of the study population were on clopidogrel or aspirin (75%); whereas, approximately 11% were on warfarin. The right internal jugular vein was the most common site of catheter insertion (87%). The adjusted rate of alteplase use was not significantly different after algorithm implementation (Part I vs. Part II relative risk: 1.10; 95% CI: $0.73 - 1.65$, $p > 0.05$). Similarly, catheter exchange rates were not significantly different in both parts of the study (1.12 vs. 1.03 per 1000 catheter-days, $p > 0.05$). Regression analysis showed that the rate of alteplase use was inversely related to the catheter age ($p < 0.05$). In a secondary analysis on a subgroup of patients with occlusion-related catheter exchanges (n = 28),

the number of alteplase administrations significantly increased with longer waiting time for catheter exchange ($p < 0.05$).

Conclusion: The hemodialysis catheter management algorithm was not effective in decreasing the rate of alteplase use.

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I would like to express my sincere thanks to my supervisor Dr. Lavern Vercaigne for his excellent guidance, encouragement, patience and friendly help. He didn't only teach me a lot of knowledge and skills related to the project but also showed me the way of thinking and solving problems in research. More importantly, he gave me valuable advice on how to become an independent and confident investigator. Without his enthusiasm and support, this work would not have been accomplished.

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List of Abbreviations

AV fistula	Arteriovenous fistula
AV graft	Arteriovenous graft
CAD	Canadian Dollar
CI	Confidence interval
CIHI	Canadian Institute for Health Information
CKD	Chronic kidney disease
COOL	Cardiovascular Thrombolytic to Open Occluded Lines
CP	Citrate period
CVC	Central venous catheter
DNA	Deoxyribonucleic Acid
DOPPS	Dialysis Outcomes and Practice Patterns Study
ESRD	End stage renal disease
FDA	Food and Drug Administration
GEE	Generalized Estimating Equations
HD	Hemodialysis
HP	Heparin period
HSC	Health Sciences Centre
K/DOQI	National Kidney Foundation's Dialysis Outcomes Quality Initiative
Kt/V	A measure of hemodialysis adequacy
MRP	Manitoba Renal Program
Qb	Catheter blood flow rate
RRT	Renal replacement therapy
RR	Relative rate
rtPA	Recombinant tissue plasminogen activator (alteplase)
SBGH	St. Boniface General Hospital
SCDU	Sherbrook Central Dialysis Unit
SOGH	Seven Oaks General Hospital
WRHA	Winnipeg Regional Health Authority

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<u>Figure 4. Fibrin sheath enclosing the outer surface of a hemodialysis catheter</u>

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INTRODUCTION

a) Epidemiology

Chronic kidney disease (CKD) is recognized as a global public health problem. (1) It is estimated that between 1.9 to 2.3 million Canadians are affected by the disease, with 100,000 living in Manitoba. (1, 2) The National Kidney Foundation classifies CKD into five stages depending on the level of kidney function primarily measured by creatinine clearance, with stage 1 the mildest, to stage 5 the most severe. (3) Patients with stage 5 CKD, or sometimes called end-stage renal disease (ESRD), have lost 85% or more of their kidney function. (3) Recent data from the Canadian Institute for Health Information (CIHI) showed that the prevalence of ESRD in Canada has climbed nearly 50% within the last decade, from 709.5 patients per million population in 1998 to 1063.6 per million population in 2007. (4) Currently, there are over 1500 Manitobans with ESRD, making Manitoba the leading Canadian province in terms of prevalent ESRD patients per million population (Figure 1). (4)

Renal replacement therapy (RRT) is essential for the management of ESRD patients. RRT can be achieved by one of three different treatment modalities; hemodialysis, peritoneal dialysis or kidney transplantation. In Canada, the majority of ESRD patients are dependent on hemodialysis (Figure 2). (5) Hemodialysis works by circulating blood outside the body through a high flux, high efficiency dialyzer that helps to remove excess fluid, urea, creatinine and other toxins from the blood. An ESRD patient will typically require this form of treatment four hours a day, three times a week, in a specialized health care facility.

Figure 1. Prevalent ESRD patients at year end, Canadian provinces, 2007 (patients per million population)*
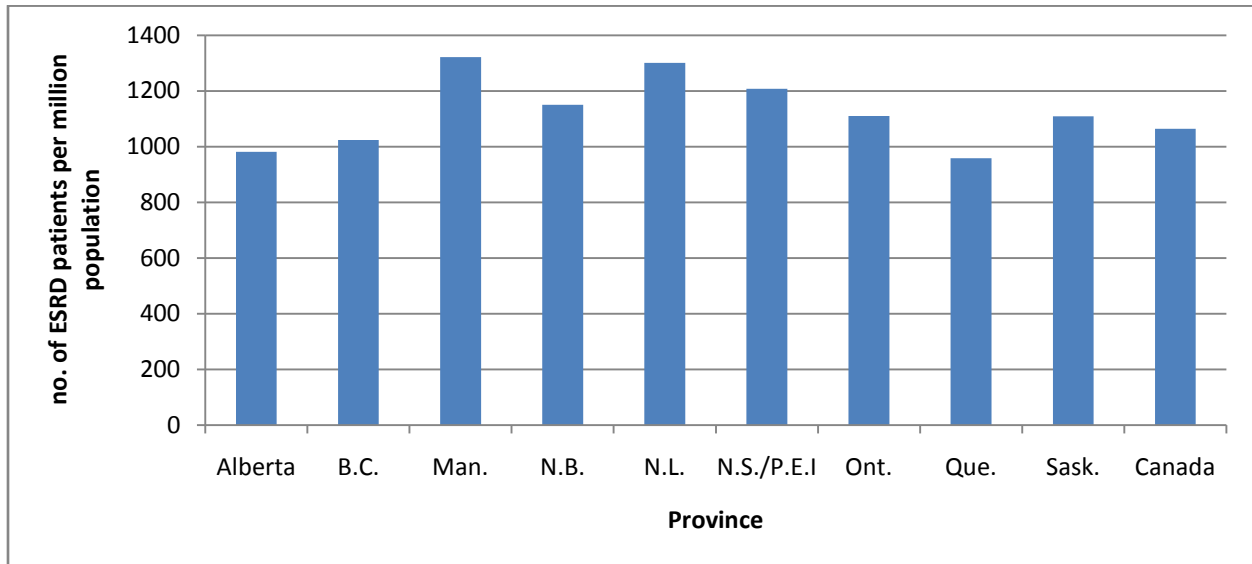
B.C.: British Columbia, Man.: Manitoba, N.B.: New Brunswick, N.L.: Newfoundland and Labrador, N.S./P.E.I.: Nova Scotia and Prince Edward Island, Ont.: Ontario, Que.: Quebec, Sask.: Saskatchewan
*Data were included from: Canadian Institute of Health Information, *2009 Annual Report-Treatment of end-stage organ failure in Canada, 1998 to 2007* (Ottawa, Ont.:CIHI, 2009).

Figure 2. Treatment modality for prevalent ESRD patients at year end, Canada, 1998-2007 (percentage)*
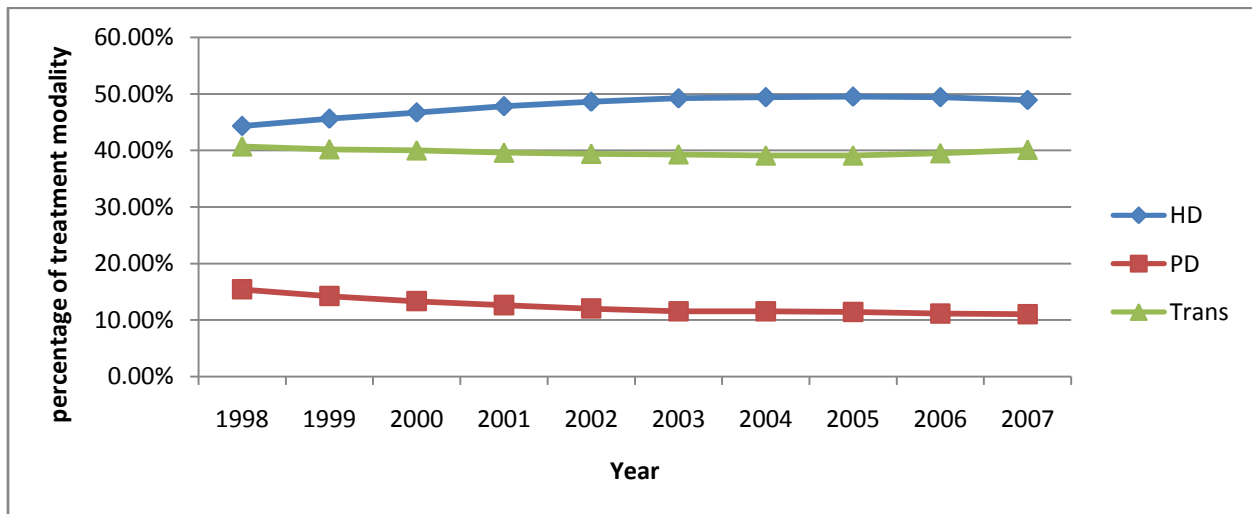
HD: hemodialysis, PD: peritoneal dialysis, Trans: kidney transplantation
*Data were included from: Canadian Institute of Health Information. *Health Conditions - Dialysis*. [cited Dec. 1st, 2009]; Available from: http://secure.cihi.ca/cihiweb/dispPage.jsp?cw_page=statistics_results_topic_dialysis_e&cw_topic=Health%20Conditions&cw_subtopic=Dialysis

b) Types of Vascular Access

In order to provide hemodialysis, every patient requires a reliable vascular access that will allow for sufficient blood flow. The source of vascular access typically takes the form of an arteriovenous (AV) fistula, AV graft, or a central venous catheter (or simply catheter). Maintaining a well-functioning vascular access is essential to deliver adequate hemodialysis therapy and to provide optimal management of ESRD. (6) Several guidelines strongly recommend AV fistulas over AV grafts and catheters because they are associated with a higher patency rate and a lower complication rate.(6-8) Indeed, the National Kidney Foundation's Dialysis Outcomes Quality Initiative (K/DOQI) recommends limiting the use of catheters as the source of vascular access to less than 10% of prevalent ESRD patients. (6)

Despite this recommendation, the Dialysis Outcomes and Practice Patterns Study III (DOPPS III), an investigation of hemodialysis patterns in 12 developed countries including Canada, indicated that this target is rarely met. (9) In fact, the prevalence of hemodialysis catheters dramatically increased in most of the countries studied during the last decade. (9) Furthermore, DOPPS III highlighted the high use of catheters in Canada compared to the United States, Japan and Europe (Figure 3). (9) The study reported up to 70% of incident patients (new starts) and 39% of prevalent patients in Canada were dependent on catheters for hemodialysis. (9) In an extended analysis to DOPPS III data, Yeates et.al. reported that more than 90% of the hemodialysis units in Canada were outside the hemodialysis catheter prevalence target of less than 10%. (10)

Figure 3. Prevalent vascular access type for hemodialysis patients in different countries, 2005-07 (percentage)*
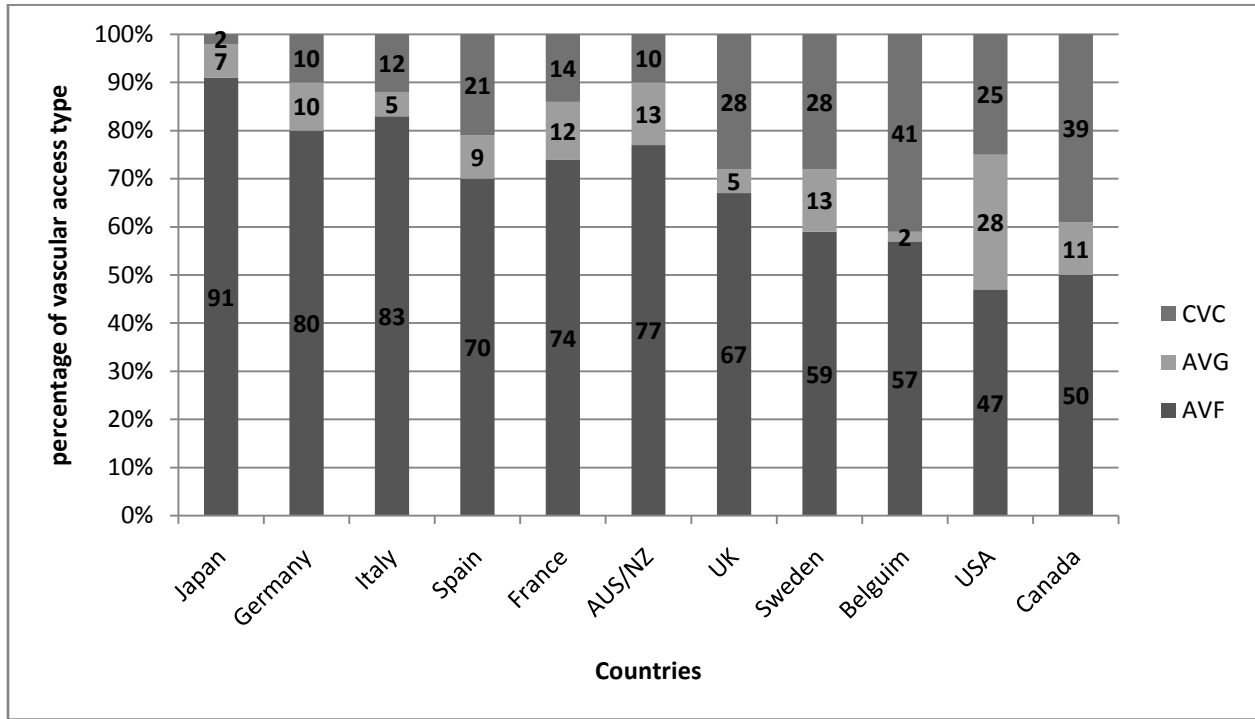
 CVC: central venous catheter, AVG: arteriovenous graft, AVF: arteriovenous fistula, AUS/NZ: Australia & New Zealand, UK: United Kingdom, USA: United States of America
*Data were included from: Ethier, J., et al., *Vascular access use and outcomes: an international perspective from the Dialysis Outcomes and Practice Patterns Study.* Nephrol Dial Transplant, 2008. **23**(10): p. 3219-26

The high prevalence of catheters in Canada as a route for hemodialysis vascular access could be attributed to the fact that catheters are suitable for immediate use following insertion; whereas, AV fistulas typically require at least 2-3 months to mature and be ready for use. (11) Thus, once an ESRD patient is identified, early referral to the vascular access surgeon is essential to allow time for AV fistula maturation and to avoid the use of permanent catheters. (11, 12) However, in recent years, the increasing percentage of patients with diabetes and vascular disease may have contributed to the high rate of AV fistula failures and more catheter insertions to replace them. (13, 14) Aging of the hemodialysis population with inadequate vasculature to create vascular access may also contribute to this problem. (13, 14) Another possible factor is the lack of enough vascular access surgeons to create AV fistulas for hemodialysis patients. (11) This was suggested when the DOPPS III study highlighted the lower number of vascular access surgeons per 100 hemodialysis patients in Canada [2.3] compared to the USA [5.9] and Europe [4.5]. (9) Additionally, patients' preference may play a role in selecting the type of vascular access. For example, using an AV fistula involves puncturing the patient's skin with two large needles before every hemodialysis treatment; a procedure that can be painful and unpleasant for the patient. Therefore, the patient may refuse an AV fistula and prefer a catheter instead. A recent cross-sectional study (n = 613) reported that approximately 12% of patients refused any AV fistula or graft creation for hemodialysis vascular access. (14) In another study, the investigators surveyed hemodialysis patients (n = 222) on their views of vascular access using a "symptoms score". (15) The study reported that patients using AV fistulas were more likely to be at least moderately bothered by pain, bleeding, bruising, swelling, and the appearance of their access than patients using catheters (p < 0.01). (15)

c) Hemodialysis Catheter Dysfunction

Catheters have become an essential form of hemodialysis vascular access especially when all other routes are unavailable or impractical; nevertheless, catheters are not problem-free. Should using a catheter for hemodialysis be considered, central venous stenosis, reduced hemodialysis adequacy, increased patient-morbidity and mortality and increased costs are among the complications that may arise. (16) However, catheter dysfunctions, along with catheter-related infections, are the most common complications. (6, 17)

The K/DOQI guidelines define catheter dysfunction as failure to maintain a catheter blood flow rate (Qb) $\geq$ 300 ml/min. (6) Catheter blood flow rates play an important role in determining hemodialysis adequacy. (18) Hemodialysis adequacy is usually measured using a ratio of urea clearance known as Kt/V with recommended Kt/V targets $\geq$ 1.2. (18) If a catheter fails to maintain a sufficient blood flow, lower Kt/V values are expected.

Several factors have been identified as a cause for catheter dysfunction. Early catheter dysfunction typically occurs with mechanical problems such as catheter kinks or cracks or malposition of the catheter tip. (6) However, the majority of catheter dysfunctions, which typically occur more than 2 weeks after catheter insertion, are attributed to catheter occlusion due to thrombosis. (6) The literature suggests that blood flow, blood coagulability and surgical trauma play a role in the process of thrombus formation; a process that begins with endothelial disruption of the vessel wall associated with surgical insertion of the catheter. (19, 20) Continual turbulence of blood flow and movement of the catheter tip inside the blood vessel may cause further endothelial damage. (19, 20) Eventually, this activates platelet adhesion and triggers coagulation and inflammatory processes leading to thrombus, i.e., a blood clot, formation at the

catheter tip. (19, 20) A thrombus may also advance into the catheter lumen attaching itself to the side walls of the catheter blocking the blood flow. (19, 20)

A fibrin sheath, a proteinaceous coating that develops around the outer surface of the catheter, is another impetus for catheter occlusion. (21, 22) Studies suggest that a fibrin sheath, which starts forming as early as 24 hours after catheter insertion, is a normal response by the body when blood is exposed to a foreign material. (21, 23) Fibrin sheath's growth begins at the point of catheter contact with the vessel wall and it advances with time along the entire length of the catheter, eventually closing over the catheter inflow and outflow holes (Figure 4). (22, 24) The prevalence of fibrin sheath is reported in the literature to be as high as 100% in hemodialysis catheters. (24) However, a fibrin sheath will only be symptomatic when it advances to the full length of the catheter to block blood flow holes at the catheter tip. (24)

Figure 4. Fibrin sheath enclosing the outer surface of a hemodialysis catheter

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Fibrin Sheath

Adapted with permission from: Mayo DJ, Pearson DC. *Chemotherapy extravasation: a consequence of fibrin sheath formation around venous access devices*. Oncol Nurs Forum. 1995 May;22(4):675-80.

d) Management of Catheter Occlusion

i) Prevention

The first step in managing catheter occlusion due to thrombosis or fibrin sheath formation is prevention. Prevention starts with selecting an appropriate catheter insertion site. The catheter insertion site associated with fewer complication and thrombosis rates is the right internal jugular vein. (16, 17, 25) Other catheter insertion sites including subclavian and femoral veins have showed higher catheter dysfunction and central venous stenosis rates.(25)

Some investigators explored the use of antithrombogenic, e.g., heparin, surface technologies on catheters, but without significant results of inhibiting thrombosis. (26) The efficacy of oral antiplatelets and systemic anticoagulants in maintaining catheter patency was also investigated, with some studies showing positive and significant results (27-29), while others reporting non-significant results. (30) Due to the lack of strong evidence of safety and efficacy, the K/DOQI guidelines discourage the routine use of aspirin or warfarin to maintain hemodialysis catheter patency. (6)

Filling the catheter lumens with a "locking solution", i.e., an anticoagulant solution, is another common practice in hemodialysis units to prevent thrombosis. Traditionally, heparin has been used as the locking solution of choice. (31) However, sodium citrate emerged as an alternative to heparin especially in patients with heparin-induced thrombocytopenia. (32-34) Despite the use of locking solutions, thrombosis is still a common complication in hemodialysis catheters. This may be attributed to the fact that a portion of the locking solution leaks out of the catheter lumens between hemodialysis sessions and is replaced by blood which remains inside

the catheter lumen until the following hemodialysis session. (22) Eventually, clotting factors in the blood may lead to thrombus formation. (22)

ii) Mechanical Intervention

Catheter exchange is an effective technique in managing occluded hemodialysis catheters especially when accompanied with fibrin sheath angioplasty. (22) The surgeon removes the old catheter and inflates a balloon to disrupt the fibrin sheath before inserting a new catheter. Fibrin sheath angioplasty is important to avoid placing the new catheter back into the retained fibrin sheath. (22)

While catheter exchange showed a very high success rate in treating catheter dysfunction, it has many limitations. (22, 35) One disadvantage is that a new wound is created with some risk of bleeding and infection. Other risks may also include arterial puncture, pneumothorax and arrhythmia. (25) Moreover, patients undergoing multiple catheter exchanges are susceptible to permanently losing their vascular access site. (25) The high costs and the need for surgical procedures are other major drawbacks. Last but not least, thrombosis may reoccur within few months of inserting a new catheter with one year patency rate reported to be around 34%. (36) Despite these limitations, catheter exchange serves as an important intervention when all other interventions fail to correct catheter occlusion, or if repeated pharmacologic interventions are needed to maintain a functioning catheter.

iii) Pharmacologic Intervention

A commonly used treatment of catheter occlusion is thrombolytic agents instilled directly into the lumens of the occluded catheter. (22) The only thrombolytic agent approved for use to clear occluded catheters in Canada and the USA is alteplase. (37) Alteplase (rtPA) is a serine protease that is manufactured using recombinant DNA technology from the naturally occurring enzyme tissue plasminogen activator. (38, 39) Alteplase dissolves a thrombus by activating plasminogen into plasmin which in turn cleaves the fibrin strands that connect red blood cells and platelets together within the thrombus (Figure 5). (38, 39)

Figure 5. Mechanism of action of alteplase (rtPA)*
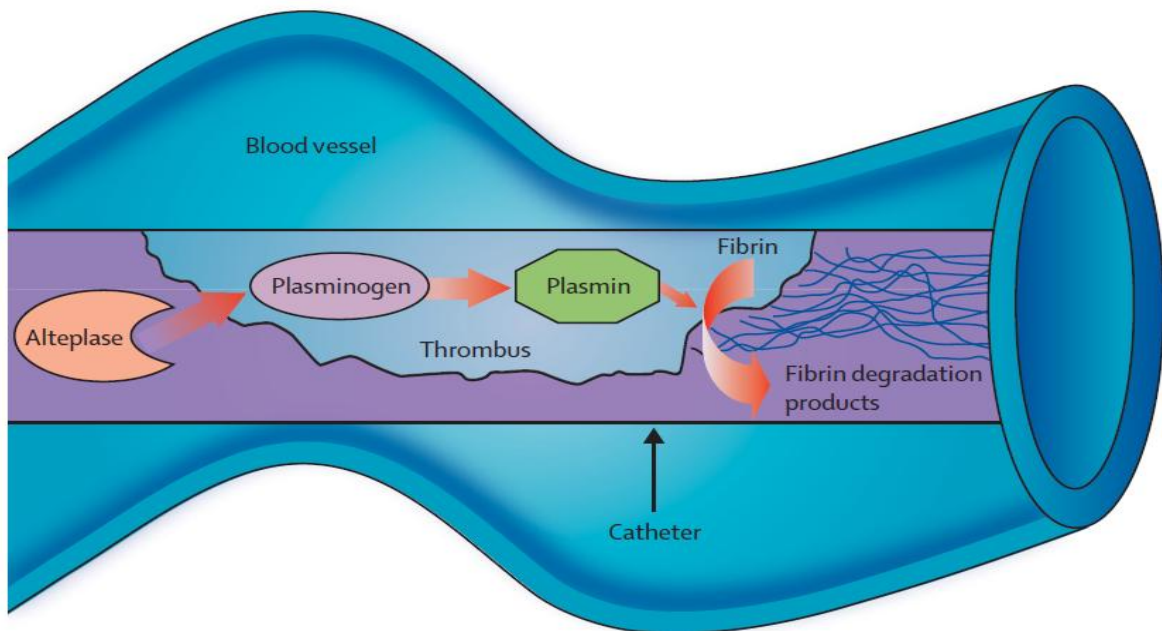
*Adapted with permission from: Baskin, J.L., et al., *Management of occlusion and thrombosis associated with long-term indwelling central venous catheters.* Lancet, 2009. 374(9684): p. 159-69.

Alteplase was licensed for use to re-canalize occluded catheters after showing successful results in two phase III clinical trials. (40) The first one was a double-blind, placebo-controlled, randomized multicentre trial known as the Cardiovascular Thrombolytic to Open Occluded Lines "COOL" trial. (41) This study examined the use of alteplase in restoring blood flow to occluded central venous catheters and access devices (no hemodialysis catheters were used). (41) Catheter occlusion was cleared after 120 min in 74% (51of 69) of patients who received a single 2 mg dose of alteplase compared with 17% (12 of 70) of patients who received the placebo (p < 0.0001). (41) A bigger proportion (90%) of patients achieved catheter clearance after receiving a second 2 mg dose of alteplase. (41) The second study was an open-label, single arm trial (COOL-2). (42) In COOL-2, 995 patients with catheter dysfunction were treated with up to two doses of alteplase (2 mg each) instilled into the catheter lumen. (42) Results from this study showed that a total of 844 (85%) of 995 patients had their catheters' function restored after up to 2 doses of alteplase. (42)

Alteplase was not only shown to be effective in treating occluded catheters, but was also proven to be safe. (41, 42) In the COOL trial, no incidence of major hemorrhage, intracranial hemorrhage or drug-related serious adverse events was reported. (41) Similarly, in the COOL-2 trial, major hemorrhage, defined as severe blood loss, blood loss requiring transfusion or blood loss causing hypotension, occurred only in 0.4% of the patients. (42) A more recent prospective non-randomized study investigated the hematologic effects of alteplase when used in hemodialysis patients (n = 10). (43) The investigators analyzed the levels of fibrin degradation products, fibrinogen, D-dimer and euglobin clot lysis time (ECLT) before and after administering alteplase and they reported no major changes in these levels. (43) Moreover, the most commonly used dose of alteplase to restore catheter patency is 2 mg per lumen which is

only a fraction of the 100 mg intravenously-administered dose used to treat myocardial infarction and pulmonary embolism. (37) In fact, if a 2 mg dose of alteplase was administered by a bolus injection directly into the systemic circulation, the concentration of the circulating alteplase would be expected to return to the endogenous circulation levels of 5-10 ng/ml within 30 minutes. (37, 40) This is due to the fact that alteplase is rapidly cleared from the plasma with a half life of less than 5 min. (37)

While it has been proven to be safe and effective in treating occluded catheters, little evidence exists describing alteplase optimal dose or administration technique. The most commonly reported administration techniques are the "push protocol", the "short dwell" and the "long dwell". (Table 1) Of note, the alteplase product monograph refers only to the short dwell technique while the hemodialysis literature discusses all techniques. (44) Studies suggest that all techniques have varying degrees of success depending upon the patient and the clinical situation. (45-52) For example, if blood cannot be aspirated at the start of a hemodialysis session or blood flow is deteriorating rapidly during a hemodialysis session, the "push protocol" or the "short dwell" are the appropriate techniques to use in this situation. The purpose of the intervention here is to correct catheter dysfunction as quickly as possible and restore optimal blood flow rates (> 300 ml/min). In another scenario, blood flow rates may deteriorate at the end of the hemodialysis session or the hemodialysis adequacy (Kt/V) is projected to be low (< 1.2). In this case, a long dwell of alteplase could be administered at the end of the hemodialysis session with a goal to achieve better blood flow rates at the beginning of the next hemodialysis session.

Table 1. Comparison between the different alteplase administration techniques in hemodialysis catheters*

	Push protocol	Short dwell	Long dwell
Procedure	- Fill each catheter with alteplase + 0.1 ml/lumen during the HD session - Push 0.3 ml normal saline/lumen every 10 min x 2 - Attempt to aspirate at 30 min	- Fill each catheter with alteplase during the HD session - Attempt to aspirate after 30-60 min	- Fill each catheter with alteplase at the end of the HD session - Attempt to aspirate at the beginning of the next HD session
Indication	- Catheter is sluggish - Qb = 0, unable to aspirate - Qb is decreasing to suboptimal level near the start of the HD session	- Catheter is sluggish - Qb = 0, unable to aspirate - Qb is decreasing to suboptimal level near the start of the HD session	- Qb is decreasing to suboptimal level near the end of the HD session - Kt/V < 1.2
Advantages	- Can be completed after 30 min - If failed, can be repeated within the same HD session - Appropriate for acute thrombolysis	- Can be completed after 30-60 min - Doesn't require close nurse attention to complete - Appropriate for acute thrombolysis	- Doesn't require close nurse attention to complete - Ideal for patients with chronic thrombosis
Disadvantages	- Requires close nurse attention to complete - The patient may receive a shorter HD session (<4 hours)	- The patient may receive a shorter HD session (< 4 hours) - If failed, may be time consuming to repeat within the same HD session	- Requires 48 hours to complete - If failed, the HD session may be rescheduled or may need further acute thrombolysis

Qb: catheter blood flow rate, HD: hemodialysis, Kt/V: a measure of hemodialysis adequacy
*For further reading, refer to: Lok, C.E. et al. *A patient-focused approach to thrombolytic use in the management of catheter malfunction.* Semin Dial, 2006. 19(5): p. 381-90

The most appropriate dose of alteplase is also unclear. Several studies used an alteplase dose of 2 mg per 2 ml to fill the catheter lumen volume with varying degrees of success (59% - 92%) (Table 2). (17, 46, 48, 51, 53-55) Other studies have investigated lower doses (e.g. 1 mg/lumen) that resulted in success rates ranging from 70% to 100% (Table 2). (45, 47, 49, 50) Of note, different studies used variable inclusion criteria and differing definitions of success and failure. For example, one study's (50) definition of failure, i.e., Qb < 300 ml/min, was still greater than another study's (51) definition of success, i.e., Qb ≥ 200 ml/min. Thus, conclusions based on comparisons between these studies should be interpreted cautiously.

Regardless of the best method to instill alteplase, or the ideal dosage regimen, recurrent thrombosis remains a significant problem with the use of hemodialysis catheters. Little and Walshe performed a 3-year prospective analysis of hemodialysis catheters in 336 patients to assess catheter patency rates and found that up to 86% of the cases receiving alteplase required additional doses within the following 14-18 days.(36) In that study, intervention with alteplase produced only 5-7 additional occlusion-free hemodialysis sessions before the same intervention was repeated. (36) The investigators concluded that whenever alteplase is required more than once in a dysfunctional catheter, recurrent thrombosis should be expected and repeated attempts of thrombolysis would only serve to treat the symptoms. (36) Inserting a new catheter would eventually be necessary in this case. (36) MacRae et al. arrived at the same conclusion in another study investigating alteplase efficacy in 60 hemodialysis patients with catheter dysfunction. (48) The authors noted that alteplase ability to restore catheter patency was short lived. (48) On average, alteplase produced only 16 days of additional hemodialysis sessions that were free of complications. (48)

The cost of alteplase is also an important issue. A 2-mg vial of alteplase costs about $64 (CAD). (Manitoba Renal Program (MRP), unpublished data; personal communication). Thus, a single alteplase treatment in both catheter lumens will cost approximately $128 (CAD). When compared to the cost of using sodium citrate 4% ($ 0.94 CAD) and heparin 10,000 U/ml ($ 6.46 CAD) as catheter locking solutions, the cost of alteplase is extremely high. (34)

Table 2. Studies investigating the use of alteplase to treat hemodialysis catheter-related thrombosis[a]

Study	Design	Alteplase dose & administration technique	Number of patients, catheters & rtPA episodes	When to intervene	Success definition	Success rate	Catheter patency[b]	Complications
Zacharias, JM et al. 2003 (53)	Non-randomized, prospective (Part 1)	Push 1mg/ml for 30 min (0.3 ml saline every 10 min)	30 patients 66 catheters (49 temporary) 116 episodes	Complete catheter occlusion: $Qb = 0$ Partial catheter occlusion: $Qb < 200$ ml/min	$Qb \geq 200$ ml/min	complete occlusion: 85% partial occlusion: 92.1%	At 1 month: 60% of the catheters (approx.)	NS
Spry, LA 2001 (51)	Non-randomized, prospective, quality assurance program	Push 1mg/1ml to catheter volume for 10 min, then push 0.3 ml tPA every 10 min to exhaust syringe volume (2.5 ml)	44 patients 113 episodes	Absence of flow, inability to aspirate lock solution, $Qb < 100$ ml/min, $Qb < 200$ with venous pressure >250 mm Hg	$Qb \geq 300$ ml/min during the next HD session	59% RIJ catheters 52% LIJ catheters 44% subclavian & temporary catheters	NS	No complications
O'Mara, NB et al. 2003 (46)	Non-randomized, prospective	Short Dwell (1mg/ml) for 30 min + additional 30 min if unsuccessful + second dose if still non-functioning	25 patients 30 catheters 62 episodes	$Qb < 250$ ml/min	Complete success: $Qb \geq 300$ ml/min Partial success: $200 \leq Qb \leq 300$ ml/min (minimum 50 ml/min increase required)	69% (complete + partial success)	Mean of 12.5 days	No bleeding complications
Macrae, JM et al. 2005 (48)	Randomized, prospective, non-blinded	Short Dwell (1hr) (1 mg/ml) vs. Long Dwell (2-3 days) (1 mg/ml)	Short Dwell: 26 patients/catheters Long Dwell: 34 patients/catheters	$Qb \leq 250$ ml/min for > 60 min or any Qb with line reversal	$Qb > 250$ ml/min	76.9% short dwell 79.4% long dwell	Median: 14 days (short dwell) 18 days (long dwell)	NS
Little, MA et al. 2002 (17)	Non-randomized, prospective	Dwell (2-8 hrs) 1mg/ml	336 patients 570 catheters 614 episodes	$Qb \leq 250$ ml/min	$Qb > 250$ ml/min	NS	Median 27 days	NS
Eyrich, H et al. 2002 (45)	Non-randomized, retrospective	Push 1mg for 60 min (0.2 ml saline every 20 min)	27 patients 43 episodes	$Qb \leq 300$ ml/min during the first 60 min	$Qb > 300$ ml/min maintained for ≥ 30 min	70%	NS	No patients experienced an adverse event

Continued: Table 2[a]

Study	Design	Alteplase dose & administration technique	Number of patients & rtPA episodes	When to intervene	Success definition	Success rate	Catheter patency[b]	Complications
Vercaigne, LM et al. 2009 (55)	Randomized, prospective, multicentre	Push 1 mg/ml for 30 min (0.3 ml saline at 10 min) vs. short dwell 2 mg/ml for 120 min	37 (push) vs. 41 (dwell)	Qb < 200 ml/min	Qb > 300 ml/min	81% Push 66% Dwell	NS	No serious adverse events within 24 hours
Daeihagh et al. 2000 (54)	Non-randomized, retrospective	Dwell (2 to 96 hours) (1 mg/ml)	22 patients 28 catheters 56 episodes	Qb < 200 ml/min	Qb ≥ 200 ml	87.5%	At 1 month: 40% (approx.)	NS
Meers, C 1999 (47)	Non-randomized, case series	Push 1mg for 40 min (with 0.2 ml saline at 20 min intervals) (14 cases) and long dwell (26 cases)	17 patients 21 catheter (9 permanent) 40 episodes	Push: poor blood flow or line spasm Long dwell: Qb = 150-200 ml/min	Ability to dialyze patients at current or next HD session who previously had catheter malfunction causing frequent alarms	97.5% (push + long dwell)	Mean of 29.7 days	No bleeding or adverse effects
Haymond, KJ et al. 2005 (49)	Non-randomized, prospective	Administer 1mg/lumen. Complete occlusion: Short dwell (60 min) Partial occlusion: long dwell Repeat once if necessary	50 patients /catheters	Qb < 300 ml/min (26 patients). Sluggish lines, inability to aspirate, or the need for line reversal (24 patients).	Qb ≥ 300 ml/min for at least 3/4 of the HD session	Overall 72% with the first dose of alteplase, 83% with the second dose	62% required a subsequent rtPA intervention with 14 days as median time to the next rtPA intervention	NS
Nguyen, TV et al. 2004 (50)	Non-randomized, case series	Administer 1.5 mg/lumen: Within dialysis short dwell (30 min) (A) vs. Pre-dialysis short dwell (B) vs. Post-dialysis long dwell (C)	No of episodes: 23 (A), 21 (B), 8 (C)	Qb < 300 ml/min	Qb > 300 ml/min and completion of hemodialysis session	Overall 94% A: 97% B: 84% C:100%	NS	NS

rtPA: alteplase, NS: not specified, Qb: catheter blood flow rate, HD: hemodialysis, CD: catheter dysfunction, R/L IJ: right/left internal jugular vein

[a]Adapted in part from: Lok, C.E. et al. *A patient-focused approach to thrombolytic use in the management of catheter malfunction.* Semin Dial, 2006. 19(5): p. 381-90

[b]Catheter patency was defined as time-free of dysfunction after receiving the 1st alteplase intervention

RATIONALE AND HYPOTHESIS

a) Study Rationale

Recurrent thrombosis remains a chronic problem associated with the use of hemodialysis catheters. In recent years, the increasing prevalence of catheters in Canada has increased the demand on recourses for managing catheter dysfunction. Thrombolytic agents, e.g. alteplase, are used as an initial option to maintain catheter patency. However, the lack of guidelines that precisely describe the optimal alteplase dose and administration technique may have negatively impacted the use of alteplase, increasing the associated costs. This problem was evident in local hemodialysis units where the use of alteplase was based on nephrologists' and nurses' personal experience instead of specific local guidelines or algorithms to manage catheter dysfunction (Dr. Lavern Vercaigne; personal communication). For example, some hemodialysis catheters were treated for dysfunction once the catheter's blood flow rate (Qb) fell below 300 ml/min, but other catheters were not treated as long as the blood flow rate was $\geq$ 250 ml/min. In addition, many catheters were prescribed "alteplase x 3", i.e., alteplase administered for three consecutive hemodialysis sessions, to manage catheter dysfunction. This pattern of practice, which isn't supported in the literature, could lead to unnecessary administration of alteplase. (6-8) For instance, if the first dose of alteplase was effective in restoring the catheter patency, the second and third doses of alteplase were still administered regardless of response to the initial dose.

Data from the Manitoba Renal Program showed that a single unit, i.e., Seven Oaks General Hospital (SOGH) hemodialysis unit, utilized more than half of all the alteplase used within MRP program. (Table 3) The SOGH hemodialysis unit provided hemodialysis treatment for about

32% (n = 185) of the patients in Winnipeg; however, this single unit used approximately 54% (CAD $246,784) of the total alteplase expenditures within Winnipeg Regional Health Authority (WRHA) hemodialysis units. (Manitoba Renal Program, unpublished data; personal communication)

The disproportionally high use of alteplase, especially in the SOGH hemodialysis unit, may potentially be improved by introducing a guideline or an algorithm that clearly specifies when and how to manage hemodialysis catheter dysfunction.

b) **Study purpose:** To design, implement and evaluate an algorithm to optimize the management of hemodialysis catheter occlusion.

c) **Hypothesis:** By implementing the hemodialysis catheter management algorithm, the rate of alteplase use will decrease compared to the previous standard of care at the study unit.

d) **Objective:** To compare the rate of alteplase use per 1000 catheter-days between Part I of the study, i.e., the previous standard of care, and Part II that involves implementation of the hemodialysis catheter management algorithm at the study unit.

e) **Outcomes:**

  i) Primary outcome: The "rate of alteplase use per 1000 catheter-days" during both parts of the study

  ii) Secondary outcome: The "catheter exchange rate per 1000 catheter-days" during both parts of the study. (This parameter may be important because failing to replace a dysfunctional catheter in a timely manner could lead to a higher alteplase use, i.e., with fewer catheter exchanges, more alteplase interventions were expected to be used to keep the catheter patency)

Table 3. Alteplase use and expenditure within Winnipeg Regional Health Authority hemodialysis units, July 1, 2007 – March 31, 2008

Hemodialysis unit	Number of patients (%) [a]	Number of alteplase vials used [b]	Total expenditure (CAD $) (%) [c]
Health Sciences Centre (HSC) central dialysis unit	144 (24.5)	1260	$80,640 (17.6)
Sherbrook Central Dialysis Unit (SCDU)	133 (22.6)	590	$37,760 (8.3)
Seven Oaks General Hospital (SOGH) hemodialysis unit	185 (31.5)	3,856	$246,784 (53.9)
St. Boniface General Hospital (SBGH) hemodialysis unit	126 (21.4)	1440	$92,160 (20.2)
Total	588 (100)	7146	$457,344 (100)

a. Number of patients as of March 28, 2008 (Manitoba Renal Program Status Report-week 13, 2008, unpublished data; personal communication)
b. Data source: Manitoba Renal Program, unpublished data; personal communication
c. Total expenditure was calculated as the number of alteplase vials used multiplied by CAD $64/vial (cost of alteplase purchase was obtained from the MRP)

METHODOLOGY AND ALGORITHM DESIGN

a) Study Design

The study had a prospective, quasi-experimental design, in 2 parts (Figure 6). Part I involved prospectively collecting baseline data on patient demographics, etiologies and co-morbidities of ESRD, and the use of antiplatelet and anticoagulant agents. Detailed information was collected regarding catheter characteristics, i.e., catheter insertion date and insertion location, and the type of intervention used to manage catheter occlusion, i.e., alteplase and/or catheter exchange (Appendix I).

Part I of the study lasted for 3 months, from December 1st 2008 to February 28th 2009. The baseline data collection period was originally planned to last for 6 months; however, the medical director of the study unit indicated the need to implement the hemodialysis catheter management algorithm as soon as possible to address the chronic problem of a disproportionally higher alteplase use at the unit. Thus, instead of a 6-month period to establish the baseline, the investigators agreed to a 3-month timeframe.

At the end of part I, interactive education sessions were provided with the participation of nephrologists, pharmacists and nurses from the study unit. These sessions explained the rationale behind the proposed algorithm and how it would help to optimize the use of alteplase at the unit. Steps involved in the management of catheter dysfunction as well as the costs accompanying the use of alteplase were also discussed. In order to assist with the algorithm implementation, nurse educators and senior nurses were involved in a day-to-day follow up with the hemodialysis nurses, providing them with one-on-one consultations on using the hemodialysis catheter

management algorithm. Furthermore, the algorithm itself was posted and distributed throughout the unit to provide an additional reminder.

Part II of the study, the intervention period, involved the implementation of the hemodialysis catheter management algorithm and prospective data collection of the same parameters outlined in Part I. Part II lasted for 6 months (March 1st – August 31st 2009).

Figure 6. Timeline of the study design
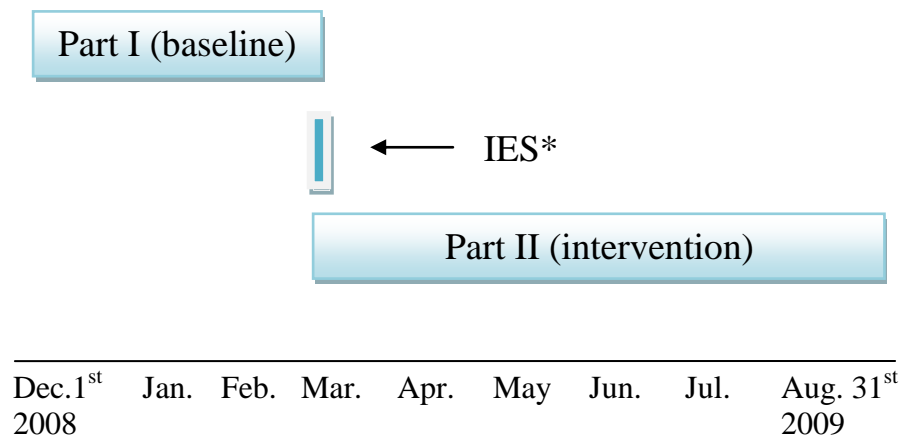
*IES: interactive educational sessions introducing the algorithm

b) Algorithm Design

According to Merriam-Webster's, an algorithm is "a procedure for solving a mathematical problem ... in a finite number of steps that frequently involves repetition of an operation". [a] (56) Similarly, a clinical algorithm was defined as "a rule of procedure for solving a clinical problem whether it is one of diagnosis or management that consists of a set of detailed, step-by-step instructions that tell the user not only which task to perform, but also the sequence in which they are to be performed". [b] (57) Clinical algorithms are often associated with clinical guidelines to organize and summarize the guideline recommendations. (58) They both act to serve the same purpose which is promoting interventions of proven benefit and discouraging ineffective ones with a goal to reduce patients' morbidity and mortality and improve the patients' quality of life. (59, 60) In addition, clinical guidelines or algorithms may act to improve the consistency of care by reducing treatment variations between patients. (59) They could also serve to reduce the cost of care by promoting more cost-effective alternatives. (61) In fact, some investigators suggested that the economic motive behind clinical guidelines or algorithms is the principal reason for their popularity. (59) Additionally, in a world having a shortage of physicians, algorithms may extend the role of nurses, pharmacists and healthcare practitioners without referring to physicians to manage some specific cases. (57)

Despite some of the potential advantages of having a clinical guideline or algorithm, they can sometimes be harmful if they are too inflexible to tailor care to the patient's case or ignore the patient's preferences. (59) In addition, they need to be kept up-to-date with the available literature and evidence; otherwise they may lead to inappropriate clinical decisions and increased associated medical costs. (59)

[a]Merriam-Webster Inc. Merriam-Webster's collegiate dictionary. 11th ed. Springfield, Mass. 2003
[b]Green G, Defoe EC, Jr. What is a clinical algorithm? Clin Pediatr (Phila) 1978;17(5):457-63

Several algorithms for identifying and managing catheter dysfunction in hemodialysis catheters have been previously published. (62) In one of them, alteplase was recommended to restore catheter patency and a second dose was reserved in case of failure of the first one. (62) However, the authors didn't specify a preferred dose or administration technique.(62) Another algorithm, suggested by Lok et al., characterized hemodialysis catheter dysfunction based on catheter blood flow rates (Qb), but didn't incorporate Kt/V (hemodialysis adequacy) as a possible indicator for catheter dysfunction. (52) The authors recommended several alteplase administration techniques depending on Qb values, but they didn't favor a particular alteplase dose or specify when to initiate catheter replacement. (52) Another algorithm has already been in use in British Columbia hemodialysis units to manage hemodialysis catheter occlusion; however, there was no formal investigation conducted to assess its safety and efficacy. (63) In Manitoba, no specific guideline or algorithm are followed in the management of hemodialysis catheter dysfunction. For this purpose, an interdisciplinary committee of nephrologists, pharmacists and nurses was formed to design an algorithm to manage patients with hemodialysis catheter dysfunction. The potential benefit of this algorithm is to reduce the rate of alteplase use; however, the literature doesn't describe the potential effect size. The authors considered a decrease by 20% in the rate of alteplase use as a potential benefit that could be important to improve alteplase use and save costs when following the algorithm. The interdisciplinary committee included: (alphabetically ordered)

- **Ahmed Abdelmoneim**, Graduate student (University of Manitoba) and pharmacist
- **Dr. Sean Armstrong**, Nephrologist and medical director (SOGH hemodialysis unit)
- **Janine Kemp**, Vascular access nurse (SOGH)
- **Robert Lajeunesse**, Nurse educator (SOGH)

- **Dr. Lisa Miller**, Nephrologist (HSC) and Chair of the Vascular Access Committee (MRP)

- **Gisele Roy**, Nurse educator (SOGH)

- **Dr. Manish Sood**, Nephrologist (SBGH)

- **Dr. Lavern Vercaigne**, Professor (Faculty of Pharmacy, University of Manitoba) and the Chair of the Renal Research and Development Committee (MRP)

- **Dr. Lori Wazny**, Nephrology pharmacist (HSC)

Details of the hemodialysis catheter management algorithm are presented below (Figure 7, with numbers for explanation):

- Catheter dysfunction was defined as "mild-moderate"[1] or "severe"[2] based on catheter's blood flow rate (Qb) and the hemodialysis adequacy (Kt/V). The algorithm aimed at diagnosing catheter dysfunction early before a thrombus or fibrin sheath got too developed and more difficult to treat by monitoring the deterioration in blood flow rate and hemodialysis adequacy.

- After ruling out problems due to catheter kinking and the patient's position, blood clots and/or fibrin sheaths were considered to be the underlying cause for catheter dysfunction.

- Nurses were instructed to follow a standard procedure whereby 10 ml of normal saline was forcefully flushed through the catheter's occluded lumens in an attempt to restore catheter patency. If failed, a 4 mg dose of alteplase (2 mg instilled into each catheter lumen) was considered.

- In the case of "mild-moderate" catheter dysfunction, the hemodialysis nurses were directed to use an alteplase "long dwell" technique post the hemodialysis treatment[3]. If catheter patency couldn't be restored, another dose of alteplase, through the "push protocol", was administered[4].

- For a "severe" catheter dysfunction, alteplase "push protocol" was instilled[5]. If failed, a nephrologist would be notified to reassess the catheter function or an alteplase "long dwell" would be ordered[6].

- Once chronic alteplase, i.e., three alteplase treatments in three hemodialysis sessions, was necessary to maintain the catheter's patency, the vascular access nurse would be notified to schedule an appointment for catheter replacement[7]. Early replacement of occluded catheter may reduce the use of alteplase and improve the vascular access function, as suggested by Little and Walshe study. (36)

- Replacing dysfunctional catheters could be limited to the availability of radiologists and vascular access surgeons. Therefore, instead of administering alteplase in dysfunctional catheters with every hemodialysis session, "rtPA dwell x 3" was used as an interdialytic dwell while the patient was waiting for his/her catheter replacement appointment[8]. This was different than the practice used in the previous standard of care as "rtPA dwell x 3", in the proposed algorithm this pattern was limited only to patients with catheter dysfunction that were not responsive to multiple administrations of alteplase and who were placed on a waiting list for catheter exchange.

- If no change in catheter function was sequentially observed with "rtPA dwell x 3", nurses were advised to revert back to heparin as a locking solution to avoid prolonged use of alteplase[9].

Figure 7. Steps involved in the hemodialysis catheter management algorithm
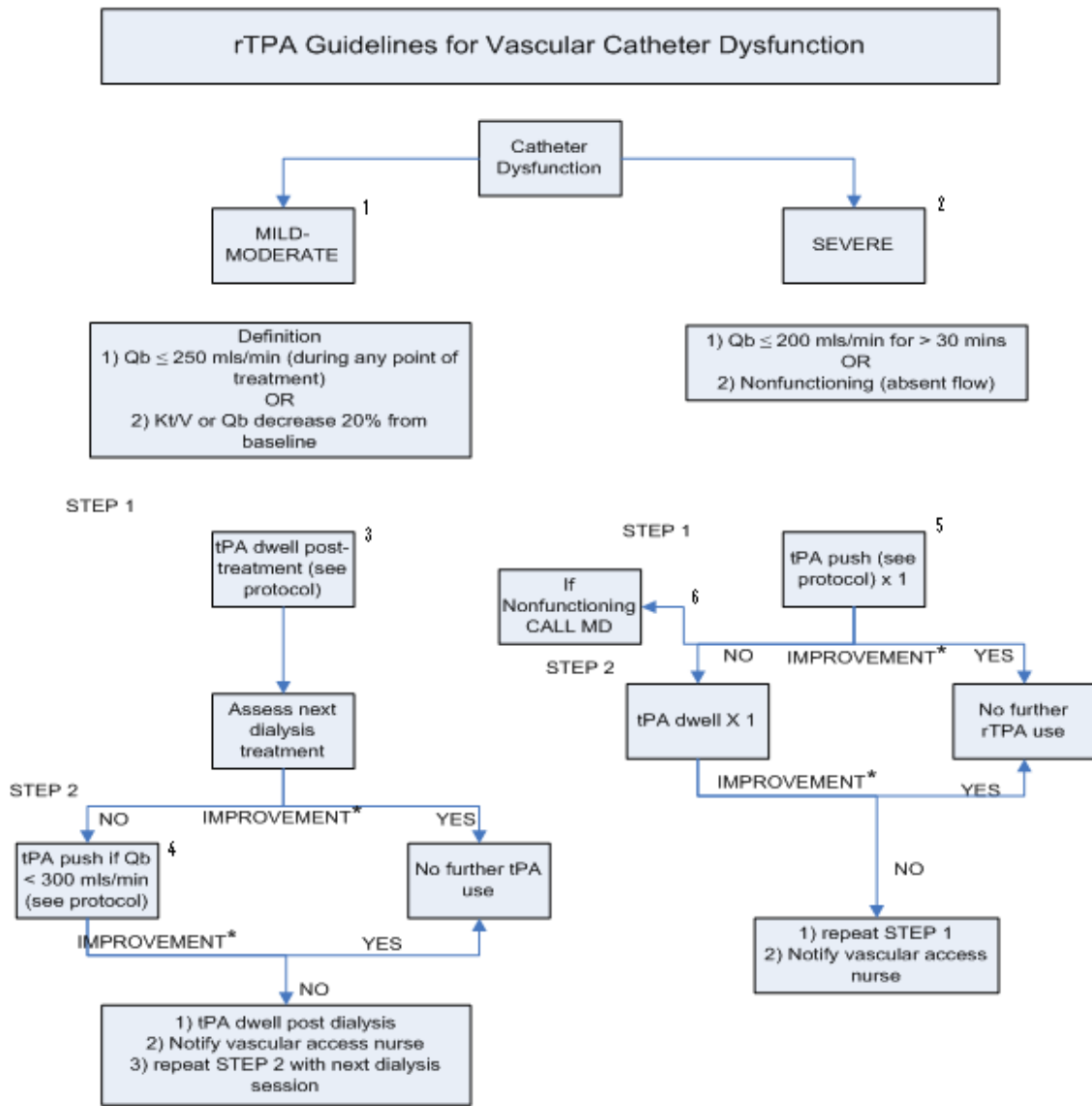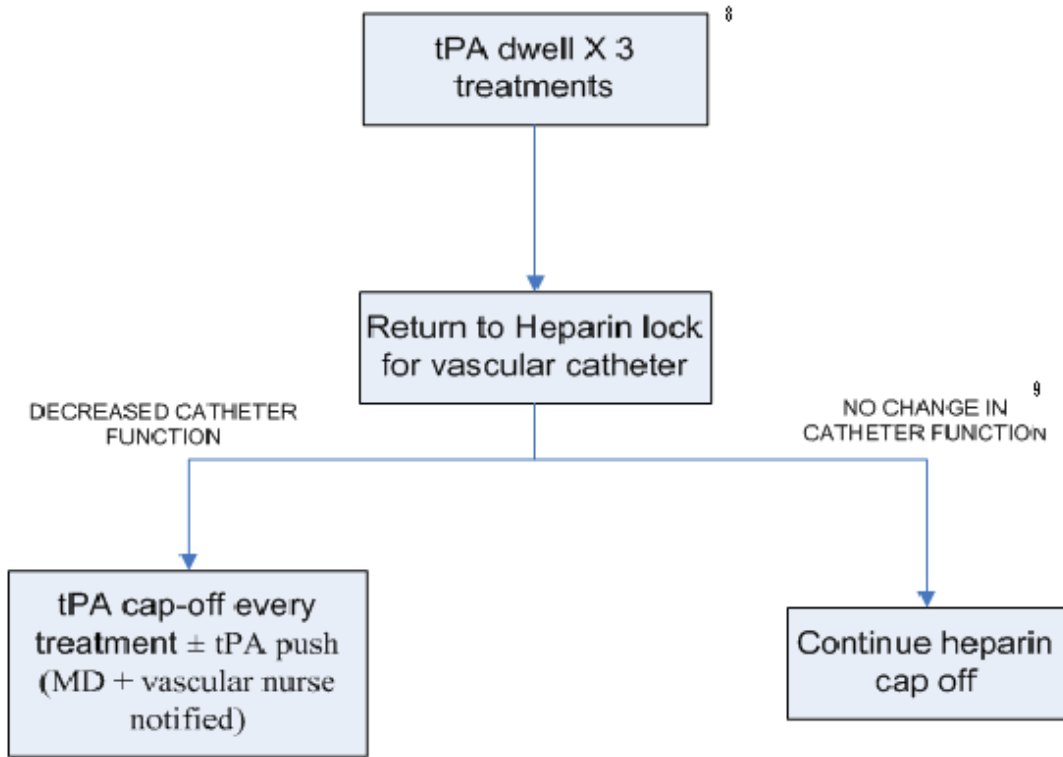

Qb: catheter blood flow rate, rtPA: alteplase, Kt/V: dialysis adequacy, tPA dwell: alteplase inserted between hemodialysis sessions (long dwell)
*Improvement: back to baseline Kt/V or Qb (equivalent of the highest value of last 3 consecutive treatments) with assessment performed within the 1st hour of the start of the hemodialysis session

Continued: Figure 7

c) Study Setting and Population

The study was carried out at the Seven Oaks General Hospital (SOGH) hemodialysis unit in Winnipeg, Manitoba, Canada. It is the largest single hemodialysis unit in Winnipeg providing hemodialysis services to nearly 185 patients. (Manitoba Renal Program Status Report-week 13, 2008, unpublished data; personal communication)

The inclusion criteria (Table 4) were hemodialysis patients, aged $\geq$ 18 years and actively using tunneled cuffed central venous catheters for hemodialysis. The exclusion criteria included patients using vascular access methods other than permanent catheters i.e., arteriovenous (AV) fistula, AV graft or temporary catheters. Catheters used for purposes other than hemodialysis, e.g., to administer medications, were excluded as well. New patients transferred to the study unit and meeting the inclusion and exclusion criteria were enrolled into the study as well.

Table 4. The study inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Hemodialysis patient	Hemodialysis through AV fistula/graft or temporary catheters
Hemodialysis through a tunneled cuffed central venous catheter	Catheters used for purposes other than dialysis, e.g., to administer medications
Adults ($\geq$ 18 years of age)	

d) Ethical Considerations

The hemodialysis catheter management algorithm was introduced as the new standard of care at the study unit. Therefore, all patients meeting the inclusion and exclusion criteria were managed using this algorithm, unless physicians had ordered alternate care. Ethics approval was

obtained from the Health Research Ethics Board, Bannatyne Campus, University of Manitoba (H2008:315) (Appendix II).

e) Statistical Analysis

Baseline patient and catheter characteristics were recorded for each patient at enrollment into the study and were described using the mean for continuous variables and proportions (%) for categorical variables. A t-test would normally be used to compare between the means and the chi-square test to compare proportions. However, it was anticipated that the majority, but not all, of patients and catheters would overlap between the two study periods; therefore, no statistical analysis was performed to test for demographic and catheter characteristics differences in the two study periods.

For the purpose of the primary and secondary outcomes, all prevalent and incident catheters were included in the analysis regardless of whether they overlapped or existed independently in each part of the study. All single or repeated alteplase interventions were recorded to calculate the rate of alteplase use. The number of catheter exchange procedures due to thrombosis or suspected fibrin sheath was used to calculate the catheter exchange rate. Catheter-days were estimated from the start of patient enrollment into the study until the end of catheter follow up. Potential reasons to stop catheter follow-up include; elective catheter removal because of the use of a mature AV fistulae or graft, using heparin-coated catheters, the start of peritoneal dialysis, kidney transplant, patient death, patient's transfer to non-study dialysis facility, or the end of the of study (August 31, 2009).

The primary and secondary outcomes of the study were expressed as a rate of events/1000 catheter-days. The rate is the number of events, e.g., alteplase count, in a population over a given period of time. (64) Rates or count data are considered to follow a Poisson distribution. (64) A

Poisson distribution, first described by the French mathematician Simeon D. Poisson (1791 –

1840), is a special kind of binomial distribution where events are considered to be very rare and

independent of each other. (65)

Rates, or count data, are modeled using a Poisson regression, an extension to traditional

regression analysis. In a Poisson regression, the outcome variable (Y), i.e., alteplase count, is

assumed to have a Poisson distribution and the logarithm of the outcome variables (log Y) to

follow a linear model. This is defined by the following equation:

$$\log E(Y) = \log (n) + a + bX$$

Where E(Y) = expected number of events, i.e., alteplase count
      n =   exposure period, i.e., catheter-days
      a =   the intercept which is the log of the mean of Y for a unit with X = 0
      b =   the slope which is the increase in log E(Y) per unit increase in X
      X =   the explanatory variable

One of the Poisson distribution's assumptions is that the mean of the data equals the

variance. (65) When this assumption is not met, i.e., variance is greater than the mean, outcomes

are considered to be overdispersed and to follow a negative binomial distribution. (64)

Overdisperssion may typically occur when the outcomes don't occur one at a time, but rather in

clusters of random size that follow a Poisson distribution, e.g., extreme count values or excess

zeros. (64)

Another important assumption in the Poisson distribution is that each event, i.e., alteplase

intervention, is independent of each other. This assumption is typically violated when repeated

measurements from the same individual are dependent on each other, i.e., one event affects the

probability of occurrence of the next. (64) This type of data is described as "correlated" or

"repeated measures" and requires a special model of analysis using "Generalized Estimating Equations" (GEE). (64, 66) This model was used in the present study because some catheters were anticipated to be carried over from Part I to Part II. Also, alteplase measurements were repeated for the same catheter, and were assumed to be correlated.

The rate of alteplase use was entered into the model as the dependent variable and adjusted for some independent variables that could potentially influence it. The use of anticoagulants, use of antiplatelet agents and the number of catheter exchanges the patient received could all be associated with a decrease in the rate of alteplase use. Whereas, waiting time for catheter exchange (calculated as the time from request for catheter exchange to the time of catheter insertion) and catheter age (estimated from the difference between "catheter insertion date" and the date at the start of patient enrollment) may increase the rate of alteplase use.

All significance testing was two-sided, and differences were considered statistically significant with a p-value < 0.05. The statistical software used was SAS (version 9.1) (SAS Institute Inc. Cary, NC, USA). A biostatistician was consulted throughout the study for discussion and analysis of the data.

RESULTS

a) Patient Demographics

One-hundred and eighty-six patients at the study unit were screened for eligibility into the study. Ninety-six (52%) patients met the inclusion and exclusion criteria. The rest of the patients (n = 90) were using either an AV fistula or AV graft for hemodialysis; hence, were not enrolled into the study. Additional 39 patients were included over the duration of the study as they presented for hemodialysis at the study unit.

Four patients were excluded from the final analysis due to protocol violations. Three of them were receiving alteplase with every hemodialysis session as per physician's orders. These patients were using their last vascular access and there was a concern that the access may be lost if they undergo a catheter exchange procedure; therefore, alteplase was administered with every hemodialysis session to keep the catheter patent. The remaining patient refused to undergo any surgical procedures, including catheter exchange; thus, he received repeated alteplase as the sole intervention.

The total number of patients included in the analysis was 131 patients, 106 patients with 8,033 catheter-days in Part I and 112 patients with 15,529 catheter-days in Part II. This included 87 patients who participated in both parts of the study (Figure 8). The characteristics of the study population are shown in Table 5. The patients' mean age was approximately 66 years and approximately 60% were women. The three most common etiologies of end stage renal disease were diabetes (50%), renal vascular disease (27%), and glomerulonephritis (14%). Hypertension

was present as a co-morbid condition in approximately 86% of the patients, followed by diabetes

(58%), and coronary artery disease (31%). The vast majority of the study population were on

clopidogrel or aspirin (75%); whereas, approximately 11% were using an anticoagulant

(warfarin).

Figure 8. Patient distribution between Part I and Part II of the study

Overlapping

Part I **Part II**

19 patients   87 patients   25 patients
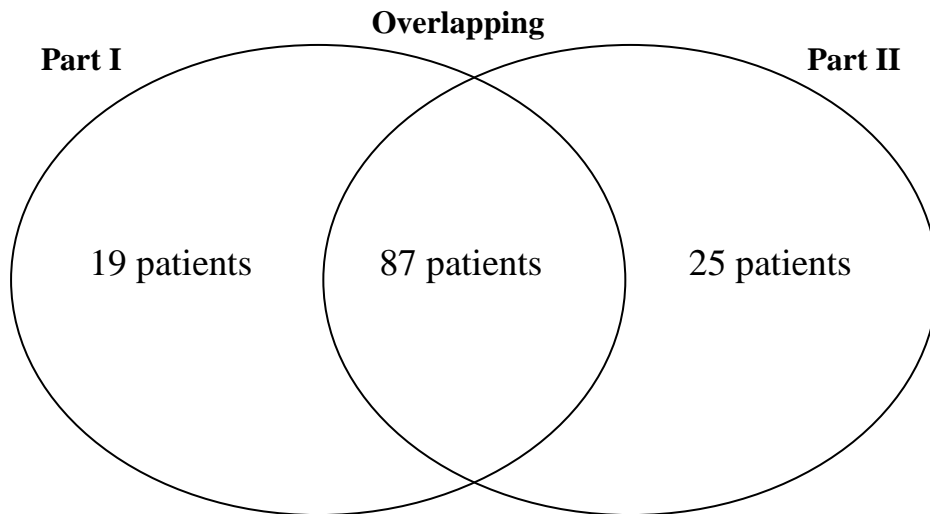
Table 5. Study population characteristics

Variable	Part I-Baseline (3 months)	Part II-Algorithm Intervention (6 months)
Patients with catheters (numbers)	106	112
Catheter-days	8,033	15,529
Mean patients' age (range)	65.5 (24 – 98)	65.9 (24 – 98)
Female (%)	66 (62.3)	67 (59.8)
Ethnicity (%)		
Caucasian	52 (49.1)	63 (56.2)
Asian	28 (26.4)	24 (21.4)
First Nation	17 (16.0)	19 (17.0)
Other	9 (8.5)	6 (5.4)
Etiology of ESRD (%)		
Diabetes	53 (50.0)	57 (50.9)
Renal vascular disease	29 (27.4)	37 (33.0)
Glomerulonephritis	15 (14.2)	16 (14.3)
Interstitial nephritis	2 (1.9)	2 (1.8)
Other[a]	9 (8.5)	7 (6.3)
Unknown	9 (8.5)	10 (8.9)
Co-morbidities (%)		
Diabetes	61 (57.5)	66 (58.9)
Hypertension	91 (85.8)	97 (86.6)
Coronary artery disease	36 (34.0)	35 (31.3)
Stroke	2 (1.9)	7 (6.3)
Congestive heart failure	17 (16.0)	16 (14.3)
Peripheral vascular disease	23 (21.7)	24 (21.4)
Hyperlipidemia	17 (16.0)	17 (15.2)
Hypothyroidism	24 (22.6)	24 (21.4)
Anticoagulant (%)	12 (11.3)	12 (10.7)
Antiplatelet (%)	79 (74.5)	84 (75.0)

ESRD: end-stage renal disease
[a]Other etiologies of ESRD were lithium toxicity, hydronephrosis, acute renal failure, obstructive uropathy, polycystic kidney disease, nephrocalcinosis

b) Patient Follow-up

There was a total of 48 patients exiting the study primarily due to AV fistulae or graft being ready for use (42 %), and transfer to a non-study dialysis unit (27 %) (Table 6). Four deaths were recorded during the study, 2 patients with sudden cardiac arrest, 1 with multisystem organ failure and 1 with retroperitoneal bleeding that was not believed to be associated with the use of alteplase. In Part II of the study, 7 patients received heparin-coated catheters at the medical director discretion's and were not followed-up thereafter.

Table 6. Reasons for patients exiting the study

Exits	Number	%
AV fistulae/graft ready	20	41.7
Deaths	4	8.3
Heparin-coated catheters	7	14.5
Kidney transplantation	1	2.1
Withdrawal of hemodialysis	2	4.2
Peritoneal dialysis	1	2.1
Transfer to non-study unit	13	27.1
Total	48	100

c) Catheter Characteristics

During the 9-month study duration, there were 172 permanent catheters used in 131 patients with each patient using at least one catheter. This was divided into 124 catheters followed up during Part I and 135 catheters in Part II. Eighty-seven of them were common between both parts of the study (Figure 9). The most common site of catheter insertion was the right internal jugular (IJ) vein (87%), followed by the left IJ (12%) and the subclavian (1%).

Figure 9. Catheter distribution between Part I and Part II of the study
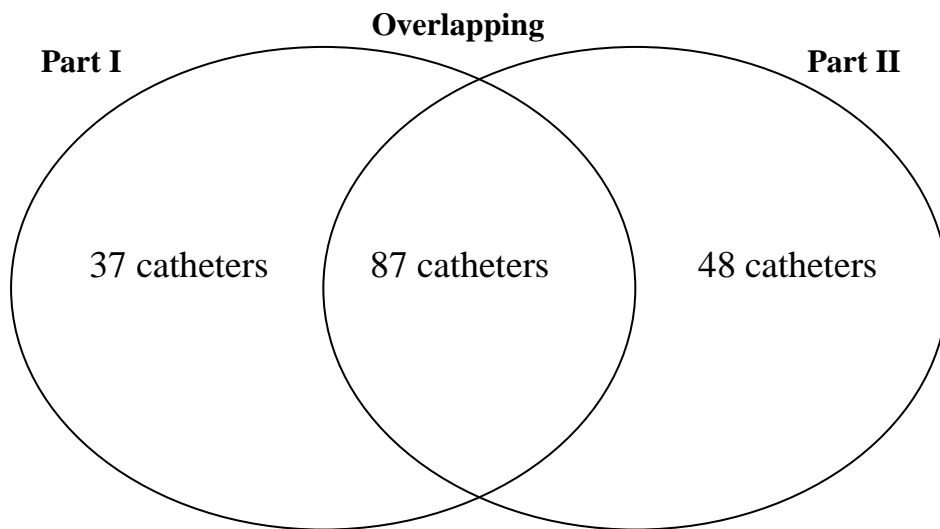
Out of the 172 permanent catheters used by the study population, 41 of them were removed and replaced with new permanent catheters (Table 7). The most common indication for catheter replacement was suspected thrombosis or fibrin sheath formation (61%), followed by accidental catheter removal (12.2%) and mechanical dysfunction (12.2%).

Table 7. Indications for catheter exchange procedures

Reason for catheter exchange	Number	%
Mechanical dysfunction (catheter too short, line not working within 2 weeks of insertion or catheter displacement)	5	12.2
Suspected thrombosis or fibrin sheath	25	61.0
Catheter-related infection	3	7.3
Central venous stenosis	1	2.4
Accidental catheter removal (catheter pulled/fall out)	5	12.2
Catheter cuff exposed	1	2.4
Not documented	1	2.4
Total	41	100

d) Primary Outcome

The total number of alteplase administrations in Part I was 316 compared to 847 in Part II. In order to estimate the primary outcome, alteplase rate per 1000 catheter days, the total number of alteplase administrations was divided by the number of catheter-days in each part of the study. The raw alteplase rate was 39.34 per 1000 catheter-days at baseline (Part I); whereas, it increased to 54.41 per 1000 catheter-days during the algorithm intervention period (Part II) (Figure 10). Nevertheless, the regression analysis showed no significant difference between the two parts of the study in terms of the rate of alteplase use ($p > 0.05$) (Table 8).

Figure 10. Comparison between the raw rates of alteplase use in Part I and Part II of the study
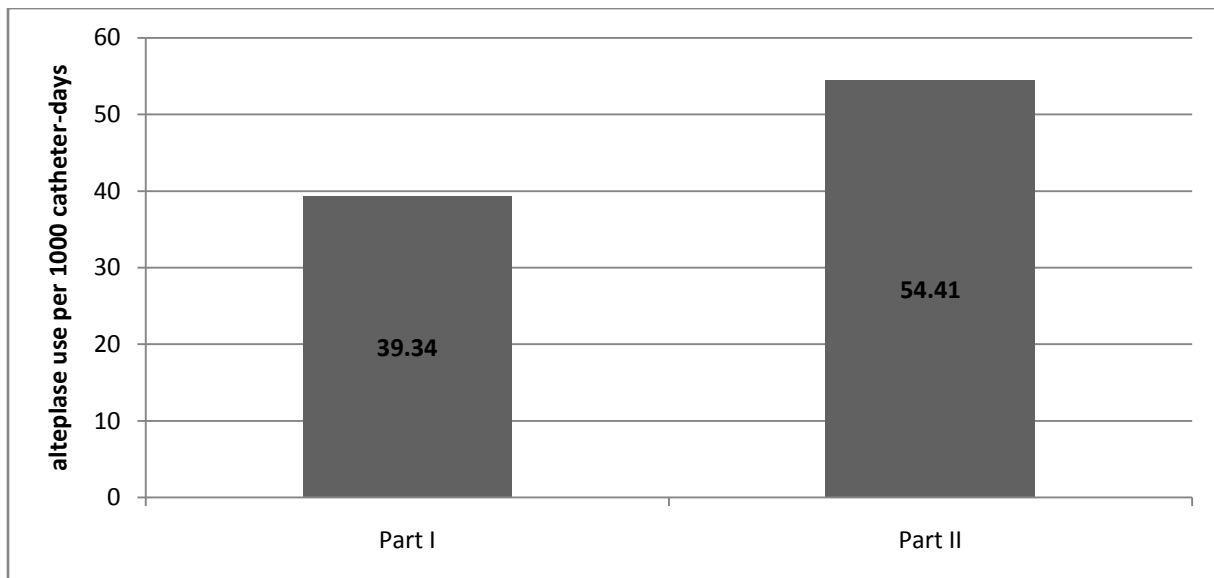
Alteplase rate: $p > 0.05$
Part I: the baseline period
Part II: the algorithm intervention period

Table 8 shows the univariate analysis of some potential predictors for the rate of alteplase use. Catheter age was a significant predictor for the rate of alteplase use as well as waiting time for catheter exchange. Other factors included in the analysis were not significant.

Table 8. Univariate regression analysis of potential factors affecting the rate of alteplase use per 1000 catheter days

Variable	Relative rate (95% CI)	p-value
Part I vs. Part II	0.59 (0.30 - 1.19)	> 0.05
Anticoagulant (Yes vs. No)	0.80 (0.36 – 1.81)	> 0.05
Antiplatelet (Yes vs. No)	0.42 (0.15 – 1.20)	> 0.05
Catheter age (in years)	0.89 (0.85 – 0.95)	< 0.05
No. of catheter exchanges	1.90 (1.29 – 2.79)	> 0.05
Waiting time for catheter exchange (in days)	1.05 (1.04 – 1.06)	< 0.05[a]

[a]For patients with catheters exchanged due to blood flow complications
CI: confidence interval

In the multivariate regression analysis, the rate of alteplase use was adjusted for the use of anticoagulants, the use of antiplatelets, catheter age, number of catheter exchanges patient received, and waiting time for catheter exchanges (Table 9). The resulted adjusted alteplase rate was lower during Part II but was not significantly different from the alteplase rate in Part I ($p > 0.05$).

It was noted from the multivariate analysis that the rate of alteplase use inversely correlated with catheter age ($p < 0.05$). Waiting time for catheter exchange had also a significant effect on the rate of alteplase use but only for a small group of patients with catheters exchanged ($n = 28$). Conversely, there was no significant relationship between the number of catheter exchanges and the rate of alteplase use. In addition, the effects of anticoagulant use and antiplatelet use were not significantly correlated with the rate of alteplase use ($p > 0.05$, $p > 0.05$, respectively).

Table 9. Multivariate regression analysis of potential factors affecting the rate of alteplase use per 1000 catheter-days

Variable	Relative Rate (95% CI)	p-value
Part I vs. Part II	1.10 (0.73 - 1.65)	> 0.05
Anticoagulant (Yes vs. No)	0.81 (0.45 – 1.47)	> 0.05
Antiplatelet (Yes vs. No)	0.86 (0.55 – 1.36)	> 0.05
Catheter age (in years)	0.80 (0.70 - 0.92)	< 0.05
No. of catheter exchanges	1.09 (0.91 - 1.31)	> 0.05
Waiting time for catheter exchange (in days)	1.04 (1.03 - 1.06)	< 0.05[a]

[a]For patients with catheters exchanged due to blood flow complications
CI: confidence interval

e) Secondary Outcome

In this study a total of 25 catheters were replaced due to suspected thrombosis or fibrin sheath, 9 in Part I and 16 in Part II. The catheter exchange rate per 1000 catheter-days, the secondary outcome, decreased in Part II compared to Part I, but was not statistically significant (1.12 vs. 1.03, $p > 0.05$) (Figure 11).

Figure 11. Comparison between the rate of catheter exchange in Part I and Part II of the study
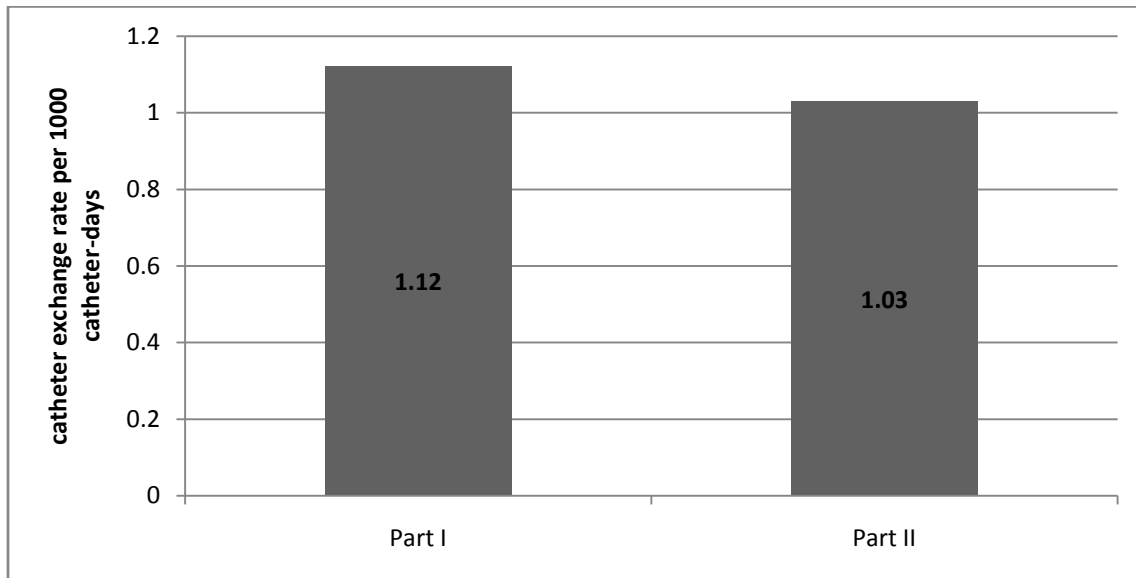
Catheter exchange rate: $p > 0.05$
Part I: the baseline period
Part II: the algorithm intervention period

f) Waiting Time

A secondary analysis was performed to investigate the effect of waiting time for catheter exchange on the number of alteplase interventions for a subgroup of patients ($n = 28$) who had orders for catheter exchange due to suspected thrombosis or fibrin sheath ($n_1 = 9$, $n_2 = 19$). This included 3 patients with pending requests for catheter exchange that were not performed before the end of the study (Aug. 31st, 2009). During the course of the study, this subgroup of patients had to wait for a total of 891 days and received 162 alteplase interventions during this time. The regression analysis showed a statistically significant increase in the number of alteplase interventions when the waiting time for catheter exchange increased ($p < 0.05$).

In a comparison between waiting time in the two parts of the study, the average waiting time per catheter was 20.36 ± 14 days in Part I of the study, while it increased to 38.42 ± 28 days in Part II ($p > 0.05$) (Figure 12). At the same time, the average alteplase use increased from 3.45 per catheter in Part I to 7.31 in Part II, but was not statistically significant ($p > 0.05$).

Figure 12. Comparison between average waiting time and alteplase interventions per catheter between Part I and Part II
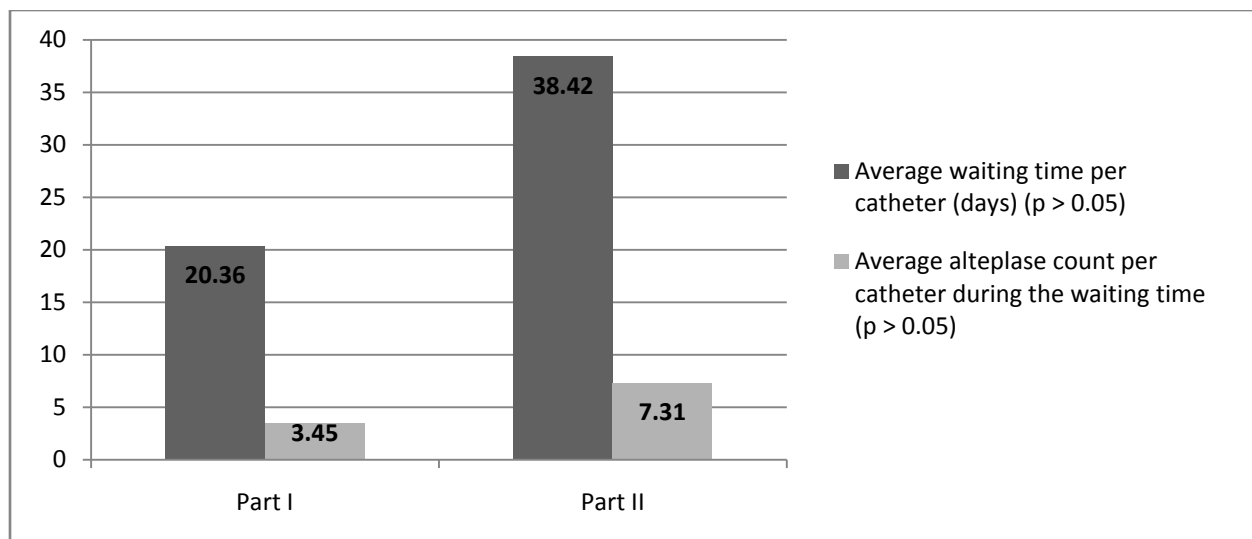
DISCUSSION

This study was the first to investigate the impact of the implementation of a step-by-step algorithm to manage hemodialysis patients with catheter occlusion. The main purpose of the study was to design, implement and evaluate an algorithm to optimize the management of hemodialysis catheter occlusion. Nevertheless, the study failed to show a statistically significant decrease in the rate of alteplase use during the algorithm implementation period. The following section discusses possible explanations and confounding factors that could have potentially affected the outcomes of the study as well as the study limitations.

a) Study Design

The design used for this study is often referred to as a quasi-experimental design. (67) A quasi-experiment is described by Shadish et al. as an experiment in which units, e.g., patients, are not assigned to conditions randomly. (67) The lack of randomization is the major limitation of such design, including this study. (67) Randomizing patients to receive or not receive the intervention is important to reduce bias and confounding factors. (67) For this reason, randomized controlled trials (RCTs) are often regarded as the gold standard for medical evidence. (68) Nevertheless, clinical practice guidelines in nephrology are often based on observational studies and expert opinions rather than RCTs. (68) A review by the Cochrane Renal Group found that RCTs make up only 1.15% of all citations in the nephrology literature between 1996 and 2002. (69) The overall paucity of RCTs in the nephrology literature is believed to be due to the numerous challenges that accompany designing and undertaking RCTs; hence, alternative designs such as quasi-experimental designs are frequently used (67, 68) Some

of the challenges of conducting a RCT for the purpose of evaluating the efficacy of the proposed algorithm are presented below.

Conducting a single unit trial with one group of patients randomized to receive the previous standard of care, and another group randomized to receive the algorithm intervention may not be appropriate due to issues of internal validity. In such situations, concerns about contamination may arise; that is, patients in the control group may receive components of the intervention making definitive conclusions about the true effect of the algorithm difficult. Conducting a multicentre trial could be more attractive; however, there are only four hemodialysis units in Winnipeg. Some of them were involved in other research studies at the time of conducting this study, e.g., Sherbrook Centre Dialysis Unit. Others were considered to have different baseline patient characteristics; e.g., HSC central dialysis unit typically provides hemodialysis of sicker patients compared to other local hemodialysis units. In addition, only the SOGH hemodialysis was presented with a disproportionally higher rate of alteplase use and comparing it with other units that had lesser baseline alteplase use may yield unreliable results due to external validity issues.

Recruitment of enough patients in the hemodialysis settings is another challenge. The nephrology literature gives some examples of RCTs that were prematurely terminated due to difficulties meeting sample size targets. (48, 55) This could be due to the limited number of hemodialysis patients meeting the usually strict inclusion and exclusion criteria of a RCT. As an example, there are less than 600 hemodialysis patients in Winnipeg with approximately 50% of them using catheters for hemodialysis (MRP, unpublished data; personal communication). After excluding patients not meeting the inclusion criteria of the study, the available number of patients is likely to be reduced. In addition, assuming that not all of the remaining patients would

sign consents to participate in the study, there may not be enough patients per treatment arm to achieve enough sample size.

Last but not least, RCTs are generally expensive to conduct and time consuming to plan, especially when considering a multicentre trial. (68) Considering all or some of these challenges, quasi-experimental designs could be more feasible to conduct rather than RCTs.

b) Algorithm Implementation

The main purpose of having a clinical guideline or algorithm is to change the clinical practice to promote safe and cost effective care. (59, 60) Nevertheless, designing and implementing clinical guidelines or algorithms doesn't ensure that the target practitioners, e.g., physicians or nurses, would alter their behavior or follow the clinical guideline or algorithm recommendations. (70) Lack of awareness of their existence, being too complicated to comprehend and follow, and disagreement with their content are the main reasons why practitioners may not follow the clinical guideline or algorithm recommendations. (70)

In the present study, interactive education sessions were provided to the hemodialysis nurses with an aim to ensure a clear understanding of the evidence and the rationale behind the implementation of the proposed algorithm. This was aided by the help of two nurse educators and senior nurses who supervised the process of algorithm implementation by providing face-to-face instructions and daily feedback to the hemodialysis nurses. Furthermore, copies of the proposed algorithm were distributed and posted within the hemodialysis unit to act as easy to access reminders. Despite this effort, it is quite challenging to ensure that all of the 60 nurses working at the study unit had the same understanding of the steps involved in the algorithm or were compliant with the algorithm recommendations. In spite of this being a potential limitation

of the study; the nurse educators and senior nurses involved in the day-to-day supervision of the algorithm implementation process were very positive about the level of nurse compliance with the algorithm.

From another prospective, the same interactive educational sessions could have served as a confounding factor to the study outcomes. These activities alone, without the algorithm, may have increased the level of awareness in the unit about the problem of catheter dysfunction leading to an increase or a decrease in the use of alteplase. Although, this could be a limitation in the study design, nurse education activities were essential to facilitate the implementation and the understanding of the proposed algorithm.

c) Statistical Analysis

Poisson regression and negative binomial (in case of Poisson overdispersion) were used to analyze the outcomes of this study, i.e., rate of alteplase use per 1000 catheter-days. The rationale behind following this statistical procedure was because rates or count data are considered to follow a Poisson distribution. (64) This was consistent with other studies that used a similar statistical model to compare the outcomes. For example, Lok et al. used "exact binomial test for Poisson distributions" to compare alteplase rates per 1000 catheter-days during two treatment periods. (32)

d) Patient Demographics

Most patients (87 out of 131) included in this study participated in both parts of the study; therefore, no statistical analysis was performed to test for differences between the two groups at baseline. Nevertheless, the generalized estimating equations model used in the analysis has taken into account the potential correlation between the subjects included in both parts of the study.

Ideally, the comparison should have been carried out between two independent patient groups; however, due to the small number of patients in the study unit and the short period of follow up, it may not be possible to have enough sample size.

There was a higher percentage of diabetes as an etiology of ESRD (50%) reported in this study compared to similar studies in Canada (18% - 28%). (32, 48) The reason for that could be attributed to Manitoba's higher percentage of First Nation hemodialysis patients compared to other provinces. (71) Several studies suggest that the First Nation ethnicity and diabetic ESRD are tied. (72, 73) Therefore, the higher percentage of First Nation ESRD patients who are diabetics may explain the overall higher percentage of diabetes in this study. Other ESRD etiologies and co-morbidities were generally similar to the results reported by other Canadian studies. (32, 48, 74)

e) Catheter Characteristics

Despite recommendations by different guidelines discouraging the use of permanent catheters for hemodialysis patients, their use remains high in Canada compared to the USA and Europe. (7-9, 75) The study unit was no exception and showed a higher catheter prevalence (52%) than the average use (39%) reported by the DOPPS III study in Canada. (9) However, the prevalence of catheters in this study was comparable with other Canadian studies reporting between 50 – 52% prevalence of catheters in hemodialysis patients. (34, 76)

The recommended catheter location is the right internal jugular vein due to the relative direct path to the superior vena cava and the right atrium. (25) Other catheter insertion sites include the subclavian and femoral veins; however, these sites are associated with higher dysfunction and

infection rates. (25) The vast majority of catheters (87%) in this study were inserted into the right internal jugular (IJ) vein in accordance with this recommendation.

f) Primary Outcome

The hemodialysis catheter management algorithm didn't decrease the rate of alteplase use in the study unit. Actually, this rate increased in Part II of the study, although this was not statistically significant (unadjusted relative rate (RR), 0.59; 95% confidence interval (CI) 0.3 – 1.19; p > 0.05). Several variables may have played a role in affecting this finding; therefore, they were adjusted for in the multivariate analysis. (77)

The first of these variables was the number of catheter exchanges the patient received. A newly inserted catheter may have less blood flow complications and longer patency rate than an occluded catheter. (22) This is not surprising since catheter dysfunction is frequently associated with a fibrin sheath that extends along the catheter lumen to block catheter blood flow holes. (21, 22) Therefore, inserting a new catheter, especially when accompanied with fibrin sheath angioplasty, should reduce recurrent occlusion caused by the fibrin sheath and the repetitive use of alteplase. (36) Little and Walshe, in their prospective analysis of 570 hemodialysis catheters, confirmed this by reporting that new catheters had a median time of 135 days before requiring intervention. Once a catheter failed, its patency decreased to 14 – 27 days. (36) Consequently, increasing the number of new catheter insertions could decrease the overall rate of alteplase use. However, this relationship was not statistically significant in the multivariate analysis (RR, 1.09; 95% CI, 0.91 - 1.31; p > 0.05).

The use of anticoagulants and antiplatelets could potentially decrease the rate of alteplase use. This relationship was suggested by previous studies showing a significant increase in

catheter patency for patients on warfarin and/or aspirin. (27) In the current study, the use of anticoagulants and the use of antiplatelets were associated with a decrease in the rate of alteplase use; however, these two relationships were not statistically significant ($p > 0.05$, $p > 0.05$, respectively).

Another variable that was accounted for in the multivariate analysis was catheter age. This variable could be important because catheters used for a long period of time may have been functioning well and producing good blood flows; therefore, they required less alteplase interventions. This characteristic was evident in the relationship between catheter age and the rate of alteplase use showed in this study in which the rate of alteplase use was inversely related to catheter age, i.e., as catheter age increased, the rate of alteplase use per 1000 catheter-days significantly decreased (RR, 0.80; 95% CI, 0.70 - 0.92; $p < 0.05$). This is in contrast to fibrin sheath forming over time to block catheter blood flow.

Waiting time for catheter exchange, i.e., the time from a request for catheter exchange to the time of a catheter insertion procedure, was also a potential confounder for the rate of alteplase use. Usually, the vascular access nurse notifies the radiology department when a catheter needs to be replaced to place the patient on a waiting list. However, waiting time for catheter exchange could be lengthy and this means that alteplase is the only intervention available to maintain the catheter's patency. In the current study, a secondary analysis on a subgroup of patients ($n_1 = 9$, $n_2 = 19$) who had orders for occlusion-related catheter exchange was performed to investigate the effect of waiting time for catheter exchange on the number of alteplase interventions. The regression analysis showed a statistically significant increase in the use of alteplase with longer waiting time for catheter exchange ($p < 0.05$). However, when the waiting time for catheter exchange was incorporated into the multivariate analysis to test its effect on the overall rate of

alteplase use for the entire cohort, it showed no significant effect ($p > 0.05$). This was expected since only a small group of patients (n = 28) had an order for catheter exchange; therefore, waiting time didn't affect the overall group rate.

After adjusting for the use of anticoagulants, the use of antiplatelets, the number of catheter exchanges, catheter age and the waiting time for catheter exchange, the rate of alteplase use per 1000 catheter-days was not influenced by the use of the hemodialysis catheter management algorithm ($p > 0.05$). This finding could have also been affected by some additional confounding factors. For example, as part of algorithm, nurses were allowed to administer alteplase to clear occluded catheters without consulting a nephrologist. Conversely, in Part I of the study, nurses were allowed only to intervene with alteplase through the push technique but the dwell technique was limited to nephrologists' orders upon the request of the hemodialysis nurse. This change in practice, i.e., nurses having easier access to alteplase, may partially explain the increase in the rate of alteplase use during Part II of the study compared to part I. Another possible explanation for the increased rate of alteplase use in Part II of the study was that the algorithm may have provided a mean to assess and identify catheter dysfunction more frequently; therefore, more alteplase interventions were necessary. It is worth to mention that the underlying cause of catheter dysfunction was not confirmed by any radiological diagnostic procedures. This was in keeping with the current practice that doesn't involve routine use of permcathogram or other similar diagnostic procedures. However, in some cases catheter dysfunction could have occurred due to some mechanical problems, e.g., catheter kink, and not due to thrombosis or fibrin sheath formation. This could explain some of the cases with alteplase failure and the need for repeated use of alteplase. However, there was no change in this practice between both parts of the study.

The rates of alteplase use per 1000 catheter-days in this study (39.34 in Part I & 54.41 in Part II) were higher than rates reported by other studies (Table 10). The reason for this is not entirely clear; however, several possible factors may play a role. Variation in patients' baseline characteristics between this study and others could be one factor. As an example, in Grudziniski et al study, more than 50% of the study population was on systemic anticoagulation, i.e., warfarin, with about 84% of them receiving it to maintain catheter patency. (34) Conversely, only 11% of the patients were taking warfarin in the current study. The reason for this smaller proportion is because the use of systemic anticoagulation was not part of the hemodialysis catheter management algorithm, and is not recommended as a routine intervention by different guidelines due to increased risk of major bleeding events. (6) Nevertheless, warfarin, especially when titrated to INR of 1.8 to 2.5, could contribute to a lower catheter dysfunction rate and a reduction in the use of alteplase. (27, 28)

Another reason for lower reported rates of alteplase use in the literature could be due to the variability in the use of catheter locking solutions between the current study and the other published studies. (32, 34) The standard orders for locking solutions at the study unit was heparin 1,000 U/ml to catheter volume and sodium citrate 4% was used instead of heparin in select cases. However, higher heparin concentrations were used in Grudizniski et al and Lok et al studies (10,000 and 5,000 U/ml, respectively). (32, 34) The use of higher concentrations of heparin could be associated with less alteplase use as reported by one study. (78) In that study, the routine concentration of heparin was decreased from 10,000 U/ml to 1,000 U/ml for patients with hemodialysis catheters. (78) At the same time, there was a significant increase in the rate of alteplase use (8.2 vs. 26.6 uses per 1000 hemodialysis sessions, $p < 0.001$). (78)

The availability of vascular access surgeons to replace dysfunctional catheters in a timely manner could be another possible factor for the observed variations in the rate of alteplase use. In the present study, the use of alteplase was significantly associated with the waiting time for catheter exchange, i.e., the longer the catheter was waiting to be exchanged; the more alteplase was required to maintain the catheter patency ($p < 0.05$). It could also be possible that other studies had vascular access surgeons readily available to replace dysfunctional catheters once it was indicated; consequently, reducing the waiting time for catheter exchange and the need for an alteplase intervention.

Finally, in the current study alteplase was mainly ordered by nurses based on their assessment of catheter dysfunction without consulting the nephrologists. This practice, which may not necessarily be the same in other studies, may have affected the rate of alteplase use. In fact, the investigators of one study assessing the efficacy of catheter locking solutions suggested that the change to nurses ordering alteplase rather than physicians may have increased the rate of alteplase use observed in their study. (78) In conclusion, all or some of the reasons discussed may explain the higher rate of alteplase use reported in this, although were not directly assessed in this study.

Table 10. Studies quoting the rates of alteplase use and catheter exchange in hemodialysis patients

Study	Design	Number of catheter-days	Rate of alteplase use (per 1000 catheter-days)	Catheter exchange rate (per 1000 catheter-days)
Lok et al. (2006) (32)	Prospective cohort	HP: 16,761 CP: 17,593	HP: 5.49 CP: 3.3	HP: 2.98 CP: 1.65
Grudzinski et al. (2006) (34)	Non-randomized, retrospective	HP: 30,925 CP: 37,139	HP: 4.1 CP: 3.23	HP: 1.81 CP: 1.88
Little and Walshe (2002) (36)	Non-randomized, prospective observation	89,216	6.88* (614 doses)	2.62* (234 catheters)
Jain et al. (2009) (26)	Non-randomized, retrospective	89 heparin-coated catheters, 86 non-coated catheters (16 months follow up)	1.8 for both types of catheters	NS
Thomas et al. (2007) (78)	Non-randomized, retrospective	Heparin I (10,000 U/ml): 3,780 Heparin II (1,000 U/ml): 2,851	Heparin I: 8.2 Heparin II: 26.6 (rates were expressed per 1000 HD sessions)	NS

NS: not specified, HP: heparin period, CP: citrate period, HD: hemodialysis
*Rates were calculated from information provided in the study

g) Secondary Outcome

The catheter exchange rate per 1000 catheter-days was lower in Part II compared to Part I, though not statistically significant (1.12 vs. 1.03, $p > 0.05$). The proposed algorithm was designed to promote early catheter exchange once chronic alteplase was indicated, i.e., 3 alteplase interventions in 3 hemodialysis treatments. The reason for following this approach was to identify catheters with chronic dysfunction early enough before the problem of dysfunction gets more severe and difficult to treat; hence, reducing the need for recurrent alteplase use. (36) Therefore, it was anticipated that catheter exchange rate would increase when following the algorithm; however, the findings of the study showed a lower catheter exchange rate in Part II, although not significant. This could be related to less vascular access surgeons and radiologists being available during Part II of the study to replace dysfunctional catheters compared to Part I. This was shown in the comparison between waiting time for catheter exchange in the two parts of the study which showed an increase from an average 20 days per catheter in Part I to 38 days in Part II. Therefore, the availability of vascular access surgeons and radiologists may explain the observed variations in catheter exchange rate between both periods of the study.

When compared to other similar studies, the overall catheter exchange rate reported in this study was lower (Table 10). The reason for that could be due to that other studies may have better access to radiology and vascular access surgeons. The lower catheter exchange rates in this study may also be a reason to explain the higher rate of alteplase use in relation to other studies.

h) Study Validity

As it has been mentioned before, randomization is important because it ensures an even distribution of known and unknown confounding factors between the comparison groups of the

study. Confounding factors represent a threat to the internal validity of a quasi-experiment as described by Shadish et al. : (67) *" Threats to internal validity are those other possible causes-reasons to think that the relationship between A and B is not causal, that it could have occurred even in the absence of the treatment, and that it could have led to the same outcomes that were observed for the treatment"**

Shadish et al. outlined nine possible threats to the internal validity when using a quasi-experimental design. The plausibility of each was assessed for their impact on this study.

1. **Ambiguous Temporal Precedence**: "Lack of clarity about which variable occurred first may yield confusion about which variable is the cause and which is the effect". This should not be a concern in this study because the algorithm was implemented first, then the outcome data were collected later.

2. **Selection**: "Systematic differences over conditions in respondent characteristics that could also cause the observed effect". Although no statistical test was performed to compare patients' baseline characteristics, most patients participated in both parts of the study. This may have ruled out systemic differences between the two patient groups of the study.

3. **History**: "Events occurring concurrently with the treatment could cause the observed effect". The main change that occurred in the study unit between the two parts of the study was the algorithm implementation. However, this process was accompanied with educational sessions to facilitate the implementation of the algorithm in the study unit. These educational sessions could represent a potential confounding factor to the outcome of this study.

4. **Maturation**: "Naturally occurring changes over time could be confused with a treatment effect". One possible maturation factor was the in the significant relationship between

*Shadish WR, Cook TD, Campbell DT. Experimental and Quasi-experimental Designs for Generalized Causal Interference. Boston, MA, USA: Houghton Mifflin Company; 2002.

the catheter age and the rate of alteplase use, i.e., as catheter age increased, the rate of

alteplase use decreased ($p < 0.05$). Nevertheless, the effect of catheter age was ruled out

statistically in the multivariate analysis.

5. **Regression**: "When units are selected for their extreme scores, they will often have less

    extreme scores on other variables". If patients were selected because of their extreme

    outcome, e.g., extremely high alteplase rate, on a single observation or measurement, they will

    be less likely to have the same extreme outcome on a subsequent observation or measurement.

    This effect was not evident in this study because the disproportionally higher use of alteplase

    reported in the study unit was the normal rate for many months before the start of this study

    and was not an extreme measurement. To further characterize this, data on alteplase use were

    collected prospectively and showed a high alteplase use. This suggested that the normal rate

    of alteplase use at the unit was already higher than other local hemodialysis units.

6. **Attrition**: "Loss of respondents to treatment or to measurement can produce artifactual effects

    if that loss is systematically correlated with conditions". Attrition could be a limitation of this

    study because the study allowed for patient drop out and yet included them in the analysis. For

    example, this was evident in Part II of the study when some patients with highly dysfunctional

    catheters were selected to receive heparin-coated catheter per discretion of the medical

    director of the study unit, therefore, they were censored. This could be perceived as omitting

    the more dysfunctional catheters. However, there is always a challenge to conduct clinical

    investigations in busy units where the priority is always to provide patient care rather than the

    investigation.

7. **Testing**: "Exposure to a test can affect scores on subsequent exposures to that test". For

    example, weighing someone may cause the person to try to lose weight on a second

measurement without any effect of the intervention. However, many measures are not reactive in the same way and Shadish et al. gave the example of the effect of testing on someone's height, e.g., a person can't alter his/her height on subsequent testing. (67) Similar to height, the main outcomes of this study, i.e., rates of alteplase use and catheter exchange, were not likely to be affected by repeated testing.

8. **Instrumentation**: "The nature of measurement can change over time or conditions in a way that could be confused with a treatment effect". All instrumentations involved in assessing the outcome, e.g., dialysis machines and catheter brand, were the same in both parts of the study. When some patients received heparin-coated catheters, they were censored in order to keep the same "instrumentation" between the two study groups.

9. **Additive and interactive threats**: "The impact of a threat can be added to that of another threat or may depend on the level of another threat". Some of the potential internal threats discussed in this section could interact with one another to magnify their total impact on the study outcomes. For example, the impact of catheter loss in Part II of the study may interact with the effect of the educational activities to produce a magnified effect on the outcomes of this study.

Opposite to the internal validity, the external validity asks the question of generalizability. (67) The algorithm investigated in this study was based on criteria generally used by all hemodialysis units, i.e., blood flow rate as an indicator for catheter dysfunction. In addition, interventions used to manage catheter occlusion, i.e., alteplase and catheter exchange, are commonly used in hemodialysis units. Therefore, there is no reason to think that this algorithm is specific only to the current study unit and not generalizable to other local and national dialysis units.

CONCLUSION

The results of this study suggest that the hemodialysis catheter management algorithm was not effective in decreasing the rate of alteplase use. Nevertheless, following a step-by-step algorithm could provide a means to assess and identify catheter dysfunction and offer a consistent treatment for every patient.

FUTURE SCOPE

- Investing more resources to improve the access to radiologists and vascular access surgeons could be an important step to reduce the rate of alteplase use through replacing dysfunctional catheters more frequently. Further study is required to better address this issue and evaluate its cost-effectiveness.

- The results of this study showed a significant indirect relationship between the rate of alteplase use and catheter age. Additional investigation could be necessary to explain why some catheters tend to perform well for a long period of time without the need for alteplase intervention and whether some patient-specific factors, e.g., coagulability profile, may determine this relationship.

- The rate of alteplase use reported in the study was higher than what have been reported by other studies. It could be worthwhile to investigate some of the potential reasons suggested in this thesis.

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Appendix I: Data Collection Form*

Enrollment Date (dd/mm/yyyy):

Demographic Data

Patient Code: SOGH				
DOB (dd/mm/yyyy):		Gender	☐ M	☐ F
Weight (kg)		Height (cm)		
Ethnicity ☐Caucasian ☐ First Nation		☐ Asian	☐Other_____	

Medical Conditions

Disease co-morbidities			ESRD Etiology		
Diabetes	☐ Y	☐ N	Diabetes	☐ Y	☐ N
Hypertension	☐ Y	☐ N	Hypertension	☐ Y	☐ N
Coronary artery disease	☐ Y	☐ N	Glomerulonephritis	☐ Y	☐ N
Stroke/transient ischemic attack	☐ Y	☐ N	Interstitial Nephritis	☐ Y	☐ N
Peripheral vascular disease	☐ Y	☐ N	Others_____		
Hyperlipidemia	☐ Y	☐ N			
Others_____					

Current anticoagulant/antiplatelets

Anticoagulant	☐ Warfarin	☐ LMWH	☐Other_____		
Antiplatelet	☐ Asprin	☐ Plavix	☐ Dipyridamole	☐ Ticlopidine	☐Other___

Catheter Characteristics

Catheter location ☐ Right ☐ Left
☐ IJ ☐ Subclavian ☐ Femoral ☐ Other_____
Catheter Insertion Date (dd/mm/yyyy):

* Data extracted from the Data Collection Form to address the objective of the study and calculate the primary and secondary outcome of the study.

Continued: Appendix I

Patient Follow-Up Form

Period I

Patient Code:

Intervention Date	rTPA (push)	rTPA (dwell)	QB $_I$ (ml/min)	QB $_{II}$ (ml/min)	Warfarin				Other Interventions
					Dose	INR	Indicat.	Complicat.	

QB $_I$: QB before intervention   QB $_{II}$: QB after intervention   INR: most recent one to intervention date

Continued: Appendix I

Period II

Intervention Date	rTPA (push)	rTPA (dwell)	QB I (ml/min)	QB II (ml/min)	Warfarin				Other Interventions
					Dose	INR	Indicat.	Complicat.	

QB $_I$: QB before intervention   QB $_{II}$: QB after intervention   INR: most recent one to intervention date

Continued: Appendix I

Period I

Patient Code:

Catheter Procedure						Hospitalization		
Request Date (d/m/y)	Procedure Date (d/m/y)	Procedure Location	Insertion Location	Reason for Procedure		Admission Date (d/m/y)	Duration of Stay	Indication
		☐ Angio ☐ OR ☐ Ward ☐ 7ODU ☐ Other_____	☐ Right ☐ Left ☐ IJ ☐ SC ☐ Femoral	☐ F. Sheath ☐ Thromb. ☐ break/crack ☐ Infection ☐ CVC Removal/why?____ ☐ Other____				☐ Bleeding ☐ CRI ☐ Other_____
								☐ Bleeding ☐ CRI ☐ Other_____
		☐ Angio ☐ OR ☐ Ward ☐ 7ODU ☐ Other_____	☐ Right ☐ Left ☐ IJ ☐ SC ☐ Femoral	☐ F. Sheath ☐ Thromb. ☐ break/crack ☐ Infection ☐ CVC Removal/why?____ ☐ Other____				☐ Bleeding ☐ CRI ☐ Other_____
		☐ Angio ☐ OR ☐ Ward ☐ 7ODU ☐ Other_____	☐ Right ☐ Left ☐ IJ ☐ SC ☐ Femoral	☐ F. Sheath ☐ Thromb. ☐ break/crack ☐ Infection ☐ CVC Removal/why?____ ☐ Other____				☐ Bleeding ☐ CRI ☐ Other_____
								☐ Bleeding ☐ CRI ☐ Other_____

Continued: Appendix I

Period II

Catheter Procedure						Hospitalization		
Request Date (d/m/y)	Procedure Date (d/m/y)	Procedure Location	Insertion Location	Reason for Procedure		Admission Date (d/m/y)	Duration of Stay	Indication
		☐ Angio ☐ OR ☐Ward ☐7ODU ☐Other_____	☐ Right ☐ Left ☐ IJ ☐ SC ☐ Femoral	☐ F. Sheath ☐ Thromb. ☐ break/crack ☐ Infection ☐ CVC Removal/why?____ ☐ Other____				☐ Bleeding ☐ CRI ☐ Other_____
								☐ Bleeding ☐ CRI ☐ Other_____
		☐ Angio ☐ OR ☐Ward ☐7ODU ☐Other_____	☐ Right ☐ Left ☐ IJ ☐ SC ☐ Femoral	☐ F. Sheath ☐ Thromb. ☐ break/crack ☐ Infection ☐ CVC Removal/why?____ ☐ Other____				☐ Bleeding ☐ CRI ☐ Other_____
		☐ Angio ☐ OR ☐Ward ☐7ODU ☐Other_____	☐ Right ☐ Left ☐ IJ ☐ SC ☐ Femoral	☐ F. Sheath ☐ Thromb. ☐ break/crack ☐ Infection ☐ CVC Removal/why?____ ☐ Other____				☐ Bleeding ☐ CRI ☐ Other_____
								☐ Bleeding ☐ CRI ☐ Other_____
								☐ Bleeding ☐ CRI ☐ Other_____

Continued: Appendix I

Kt/V Follow-Up

Patient Code:

Period I

Date (d/m/y)	Kt/V

Period II

Date (d/m/y)	Kt/V

Date (d/m/y)	Kt/V

Appendix II: Ethics Approval

BANNATYNE CAMPUS
Research Ethics Boards

UNIVERSITY OF MANITOBA

P126-770 Bannatyne Avenue
Winnipeg, Manitoba
Canada R3E 0W3
Tel: (204) 789-3255
Fax: (204) 789-3414

APPROVAL FORM

Principal Investigator: **Dr. L. Vercaigne**

Ethics Reference Number: H2008:315
Date of Approval: November 14, 2008
Date of Expiry: November 14, 2009

Protocol Title: Optimizing the Management of Catheter Occlusions in Hemodialysis Patients

The following is/are approved for use:

- Protocol as submitted November 4, 2008
- Data Collection Forms submitted November 4, 2008

The above underwent expedited review and was **approved as submitted** on November 14, 2008 by Dr. John Arnett, Ph.D., C. Psych., Health Research Ethics Board, Bannatyne Campus, University of Manitoba on behalf of the committee per your submission dated November 4, 2008. The Research Ethics Board is organized and operates according to Health Canada/ICH Good Clinical Practices, Tri-Council Policy Statement, and the applicable laws and regulations of Manitoba. The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the *Food and Drug Regulations*.

This approval is valid for one year only. A study status report must be submitted annually and must accompany your request for re-approval. Any significant changes of the protocol and informed consent form should be reported to the Chair for consideration in advance of implementation of such changes. The REB must be notified regarding discontinuation or study closure.

This approval is for the ethics of human use only. For the logistics of performing the study, approval must be sought form the relevant institution, if required.

Sincerely yours,

John Arnett, Ph.D., C. Psych.
Chair, Health Research Ethics Board
Bannatyne Campus

Please quote the above Ethics Reference Number on all correspondence.
Inquiries should be directed to REB Secretary
Telephone: (204) 789-3255 / Fax: (204) 789-3414

www.umanitoba.ca/faculties/medicine/research/ethics

Appendix III: SAS Codes

This is a sample of some of the codes used to run the regression analysis of the study using the SAS software (version 9.1) (SAS Institute Inc. Cary, NC, USA).

```
proc genmod data=saied.jan27;
 class patient_id catheter_id;
 model newTPA= part cath_ex_tot waiting_time cathageyear patage /link=log d=nb offset =
logtar type3 covb lrci;
 repeated subject=patient_id/type=cs covb;
 title 'analysis of TPA rates, new cath_ex_tot results';
run;

proc genmod data=saied.jan19;
 class catheter_id ;
 model TPA_count_while_waiting = Waiting_Time /link=log d=nb /*offset = logtar*/ type3
covb lrci;
 title 'analysis of TPA rates, only the patients waiting for orders are in';
run;

proc genmod data=procedures_model;
 class patient_id part ;
 model procs = part  /*angio antiplatelet*//link=log d=p type3 scale=deviance;
 repeated subject=patient_id;
 title 'analysis of procedure rates';
run;
```