

Initial Clinical Experience with a Symmetric Tip Tunneled Hemodialysis Catheter Without Side Holes

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The purpose of this article is to assess the performance and safety of a novel, symmetric, side-hole-free tunneled cuffed catheter hypothesized to sustain adequate flow without the need for side holes. Between November 2016 and January 2019, Pristine hemodialysis catheters were placed *de novo* in 45 end-stage renal disease patients (27 males and 18 females) at a single investigational site. Forty-one catheters were placed in the right and four in the left internal jugular vein. There were no incidents of insertion failure. Patients had dialysis three times per week and were followed at four investigational sites. Nominal catheter flows, incidence of poor flow, and catheter-related infections were recorded at each dialysis session and analyzed. The average follow-up time was 161.69 days for a total of 7116 catheter days. Nine patients died from reasons unrelated to the catheter and one patient switched to fistula. Four patients had poor flows necessitating catheter replacement. Four patients had catheter-related bloodstream infections which resolved with antibiotics. These equate to 0.56 events per 1000 catheter days. Catheter survival was 100%, 97.6%, and 89.7% at 30, 90, and 180 days, respectively. The initial clinical assessment of the symmetric Pristine hemodialysis catheter featuring a Y-tip devoid of side holes revealed good catheter performance and survival and a low complication rate. *ASAIO Journal* 2021; 67;1257–1262

Key Words: dialysis catheter, hemodialysis

A well-functioning vascular access is a prerequisite for adequate blood flow rate (BFR) to allow successful hemodialysis.¹ Failure to maintain an adequate BFR may lead to complications and hospitalization of hemodialysis patients and, in some cases, may result in death.¹ The native arteriovenous fistula (AVF) remains the recommended first choice for vascular access, in Europe and in the United States, due to a more

frequent association of synthetic means of vascular access, especially central venous catheters (CVC), with infectious and thrombotic complications.^{1–3} The National Kidney Foundation's (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) remains adamant with regard to this recommendation, but recognizes that selection bias and confounding effects may be held accountable, to some extent, for CVCs being a more complication-ridden alternative.^{4–6}

Despite the KDOQI recommendations and the Fistula First Breakthrough Initiative program that commenced in 2003,⁷ the use of CVCs in the United States shows no signs of deceleration in the past two decades. More than 80% of patients still receive a CVC at hemodialysis initiation, much as it had been 15 years ago.^{8,9} Almost 70% still use catheters 90 days later.^{8,9} An apparent increase in dependency on CVCs for hemodialysis in the European Economic Area^{10–12} attests to the universality of this treatment paradigm, rather than to an idiosyncratic *modus operandi* of the American healthcare system.

The most likely cause for a low BFR achieved with CVCs is thrombosis of the catheter and formation of a fibrin sheath, accounting for access loss in 30% to 40% of patients.¹ In a bid to curb the rate of complications, side holes were introduced in the design of the CVC distal tip with the intent to support flow in the case of thrombotic obstruction or sheathing of the end hole.¹³ Unfortunately, having been implicated in promotion of thrombosis by serving as anchors for irretrievable blood clots, side holes have since earned a reputation as a double-edged sword.¹⁴

The Pristine hemodialysis catheter (Pristine Access Technologies Ltd., Israel) has a split, symmetrical, side-hole-free tip designed to be placed in the upper right atrium and oriented in the anterior-posterior position (**Figure 1**). In a limited animal study, the Pristine hemodialysis catheter was largely superior to a symmetric tip catheter, which features side holes at its tip, in impeding clot formation.¹⁵ Contrary to the comparator, the Pristine hemodialysis catheter also allowed for complete aspiration of the intraluminal thrombus which accumulated in the catheter tips.

This study assessed the efficacy and safety of the Pristine hemodialysis catheter in providing sustainable vascular access in hemodialysis patients.

Materials and Methods

This was a prospective, nonrandomized, open-label study. Following an institutional ethics committee approval, patients were recruited between November 2016 and January 2019. Informed consent was obtained from all participants. Catheters were inserted by six operators (one surgeon, one radiologist, and four nephrologists). Dialysis treatments were delivered, and follow-up visits were performed, according to the standard dialysis treatment common practice, at four locations in the Dominican Republic.

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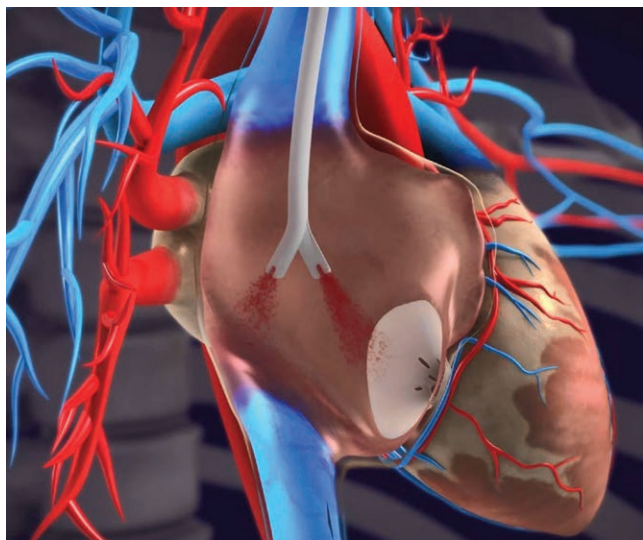


Figure 1. Illustration of the Pristine hemodialysis catheter tip orientation in the right atrium.

Subjects

Adult men and women 18 years of age or older diagnosed with end-stage renal disease or acute renal failure in need of hemodialysis through a tunneled CVC could be recruited to the study if they had a patent right internal or external jugular vein (RIJV and REJV, respectively) or left internal jugular vein, had no clinical or radiographic evidence of superior vena cava narrowing, and their treatment plan required chronic hemodialysis treatments three times per week for a minimum of 90 days. All subjects had to be able to understand and sign the consent form. Main reasons for ineligibility for the study included known central venous stenosis, platelet count $<50 \times 10^9/L$, which could not be corrected with platelet transfusion, active infection at the time of enrollment, presence of bacteremia or infected AVF or graft (AVG) within 7 days before enrollment, absolute neutrophil count $<1.5 \times 10^9/L$, known sensitivity to heparin or previous incidence of heparin-induced thrombocytopenia, and uncontrolled abnormal coagulation parameters. Other exclusion criteria were known or suspected pregnancy or pregnancy intent during the study period, breastfeeding, concurrent enrollment in any other trial, and inability or unwillingness to commit to follow-up visits and study procedures.

Forty-six subjects with end-stage renal disease signed informed consent for the study. Sixty-one percent (28/46) of them were male. The mean age of subjects was 52.3. Thirty-six subjects (78.3%) were under 65 and 10 (21.7%)—between 65 and 79 years of age. Demographics and medical history are summarized in **Table 1**. Contact with one male subject was lost before catheter insertion.

Catheter Insertion

Following local anesthesia of entry site, an introducer needle was inserted into the vein under ultrasound visualization. A 0.038 in. J/Straight stainless-steel guidewire was then inserted, and the introducer needle was removed. In the next steps, the area of the planned under-the-skin tunnel was locally anesthetized, the skin was cut with a scalpel at both

Table 1. Subject Demographics, Baseline Data, and Medical History

	N	Mean (SD; Range)
Demographics		
Age at initiation	46	52.3 (14.58; 21.0–74.0)
Weight (kg)	45	65.0 (12.08; 41.0–92.0)
Height (cm)	45	164.0 (10.92; 146.0–193.0)
BMI (calc)	45	24.3 (4.78; 16.1–35.4)
Medical history		
	N	%
Smoking history		
Never	31	67.39
Past	15	32.61
Hypertension history		
No	4	8.70
Yes	42	91.30
Diabetes mellitus history		
No	23	50.00
Yes	23	50.00
Reason for renal failure		
Diabetes	11	23.91
Glomerulonephritis	5	10.87
Hypertension	28	60.87
Hypertension and diabetes	1	2.17
Other	1	2.17

ends of the intended tunnel, and the holes were widened with curved Kelly forceps. The Pristine hemodialysis catheter was attached to the proximal end of its tunneler which was then inserted under the skin, leading the Pristine hemodialysis catheter through the tunnel created. The tunneler was then separated from the catheter, and the latter was positioned with its polyester cuff under the skin. The access hole to the vein was widened with 10-14-Fr dilators threaded one after the other over the guidewire. A peel-away sheath was inserted into the vein over the guidewire, the dilators and the guidewire were removed, and the Pristine hemodialysis catheter was introduced into the vein through the peel-away sheath (**Figure 2**) while maintaining the anterior-posterior orientation of the tip (**Figure 3**). The peel-away sheath was then extracted and both lumens of the Pristine hemodialysis catheter were forcefully aspirated with blood several times, using a 20-ml syringe. If there was difficulty aspirating, that is, if the syringe would not fill in under 2 seconds, the catheter was pulled back 2 cm until syringe filling time of 2 seconds or less was achieved for both lumens.¹⁶ The catheter was then flushed with normal saline. X-ray imaging was performed to confirm tip placement in the mid- to upper right atrium by anatomic position *versus* the cardiac shadow. Heparin lock was added to each lumen according to the amount indicated on the lumen, and the extension legs of the catheter were clamped. A sterile sealing cap was attached to the Luer adapters of the lumens. Finally, the insertion site was closed around the catheter and the Y-hub was sutured to the skin. Catheter position was again confirmed by x-ray examination.

Treatment and Follow-Up

Patients had dialysis three times per week for 6 months after insertion of the Pristine hemodialysis catheter. Nominal catheter flows, incidence of poor flows, and catheter-related infections were recorded at each dialysis session and analyzed.

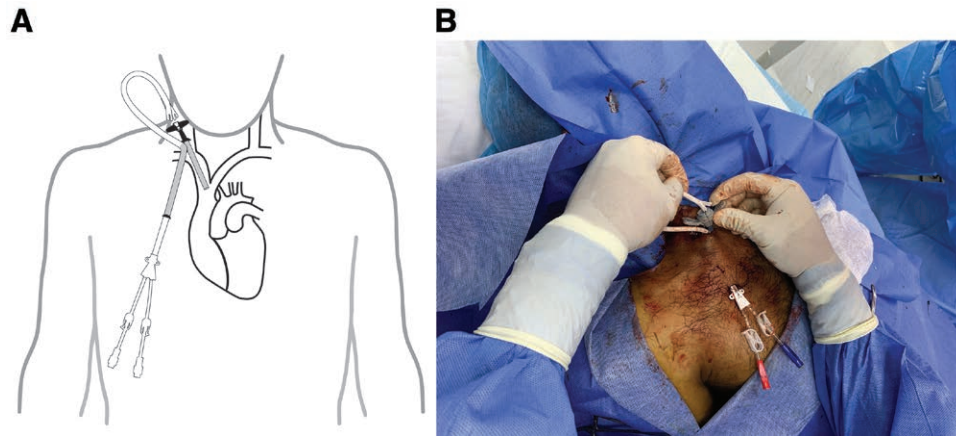


Figure 2. Insertion and right-atrium positioning of the Pristine hemodialysis catheter. **A:** Illustration. **B:** Image of the Pristine hemodialysis catheter inserted into the peel-away sheath.

Outcomes

The primary study endpoint was primary patency at 30 days following the catheter insertion. Primary patency was defined as a catheter patency, which provides adequate hemodialysis (BFR > 300 ml/min; based on average dialysis blood flow, as calculated by the dialysis machine) without need for interventions intended to maintain flow or correct device failure, that is, tissue plasminogen activator infusions, fibrin sheath stripping, or catheter exchange. Secondary endpoints included patency assessments at 60 and 180 days.

Safety Analysis

All adverse events that occurred until the end of the follow-up, whether considered related to the study device and/or procedure or not, were reported, coded, and mapped to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v. 5.0. Safety analyses were conducted by reviewing safety listings and narratives.

Statistical Analysis

Continuous variables were summarized by a mean, SD, minimum, median and maximum, and categorical variables by a

count and percentage. Two-sample *t*-test was used for comparison of means (continuous variables), and Fisher's exact test was used for comparison of proportions (categorical variables).

Time to catheter malfunction (loss of patency) was presented in a Kaplan–Meier curve. Patency probabilities at 30, 60, 90, 120, and 180 days were estimated from the curve and presented with 95% confidence intervals.

Results

Pristine hemodialysis catheters were placed in 45 subjects. Four catheters were inserted in the left internal jugular vein. All other catheters were inserted in the RIJV. Twenty-nine catheters were 19 cm in length, 12 catheters were 23 cm, and 4 catheters were 28 cm. All but one were inserted in subjects who had acute catheters before participation in this study. One subject was lost to follow up before receiving the first dialysis treatment and was excluded from analysis.

None of the Pristine hemodialysis catheters implanted in the 44 subjects eligible for analysis were occluded at 30 days after implantation; and infusions of tissue plasminogen activator, fibrin sheath stripping, or catheter exchange were not required in any of the subjects. Consequently, the primary patency was 100% at this mark.

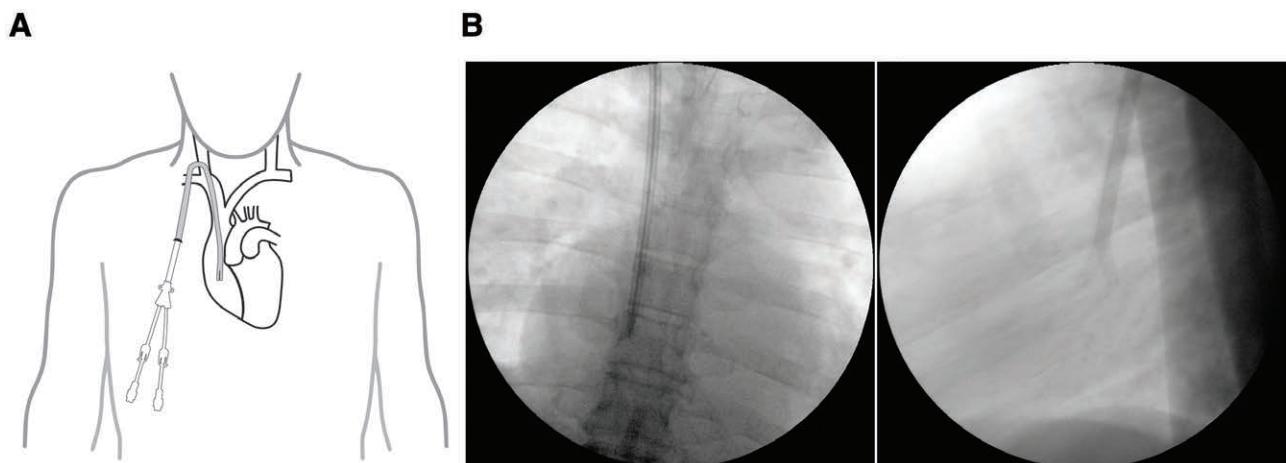


Figure 3. Insertion and right-atrium positioning of the Pristine hemodialysis catheter. **A:** Illustration. **B:** X-ray images in the anterior-posterior and lateral projection of the Pristine hemodialysis catheter preferred orientation in the right atrium.

Of the 14 subjects who did not complete the protocol-specified follow-up period, one left the study when his AVF has matured, after 155 days of follow-up. Nine subjects died during the 6 months of treatment and follow-up, all of causes unrelated to the investigational device or procedure. Lack of catheter patency was the reason for early termination in four subjects. Removal of the catheters was uneventful in all four subjects. The mean catheter survival time was 161.69 days (SE = 2.934). The Kaplan–Meier curve of time to occlusion of the Pristine hemodialysis catheter within 6 months post-implantation is depicted in **Figure 4**. The mean Kaplan–Meier estimates of patency probability of the Pristine hemodialysis catheter are presented in **Table 2**, and the true binary/proportion analysis of patency is shown in **Table 3**. Eventually, the 180-day patency probability was 89.7%.

Four events of catheter-related bloodstream infection (CRBSI; defined as one positive blood culture without obvious source) occurred and were successfully resolved with antibiotic therapy. Two incidents of local infection were reported. The calculated rates of systemic and local infection events per 1000 days are shown in **Table 4**. Other adverse events were abdominal abscess (1), transient fever of unknown origin (2), and transient loss of catheter patency (1), which was successfully treated with DuraLock-C catheter lock solution (4% sodium citrate).

Discussion

Catheter failures due to low BFR or occlusion are common, and their reported rate and timing depend, to some extent, on the definition of failure.⁶ The 2006 NKF Vascular Access Work Group guidelines advocated that assessment of catheter performance should take into account the dialyzer BFR of 300 ml/min achieved, factored by the prepump arterial limb pressure.¹

Table 2. Kaplan–Maier Estimated Probability of Primary Patency of the Pristine hemodialysis Catheter Within 6 Months of Implantation

Time (Days)	Kaplan–Maier Estimated Probability of Primary Patency (%)	Lower 95% Confidence Limit (%)	Upper 95% Confidence Limit (%)
30	100.0		
60	100.0		
90	97.6	84.3	99.7
120	95.0	81.6	98.7
180	89.7	74.7	96.0

Table 3. True Binary/Proportion Analysis of Patency of the Pristine Hemodialysis Catheter

30 days			
Proportion = 1.00			
Type	95% Confidence Limits		
Wilson	0.92		1.00
60 days			
Proportion = 1.00			
Type	95% Confidence Limits		
Wilson	0.92		1.00
6 months			
Proportion = 0.91			
Type	95% Confidence Limits		
Wilson	0.79		0.96

This recommendation was consistent with the earlier guidelines of the American College of Radiology¹⁷ and reporting standards of the Society of Interventional Radiology¹⁸ and of a joint committee of several surgical societies.¹⁹ The requirement for dialyzer-delivered BFRs greater than 300 ml/min in the adult practice reverberated beyond the United States. For

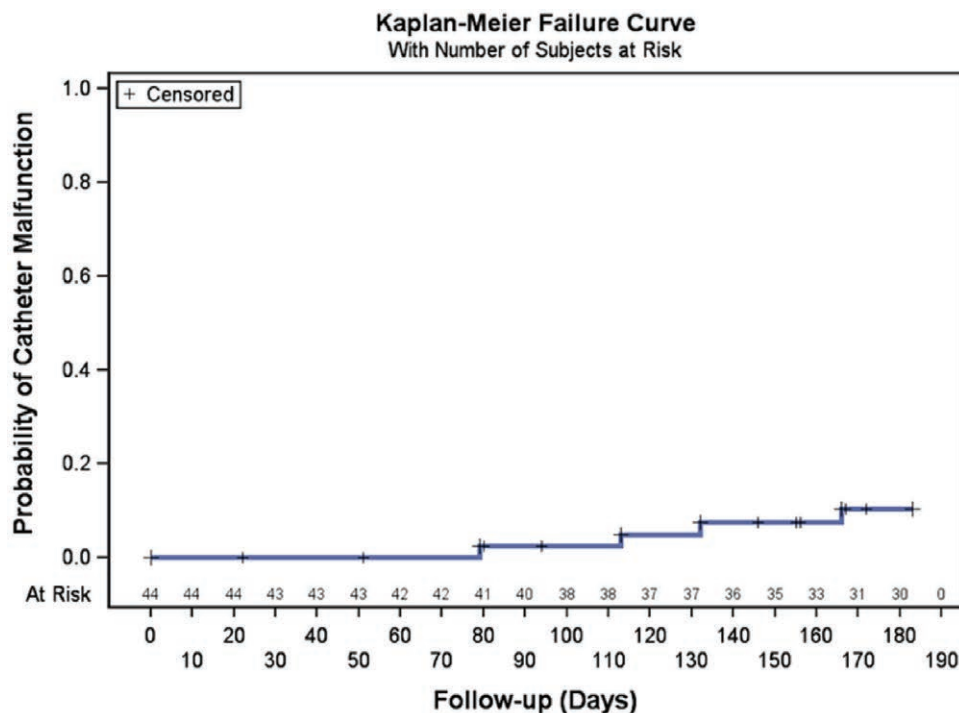


Figure 4. Kaplan–Meier curve—time to catheter occlusion. All subjects reaching the end of the protocol-specified 6-month-long follow-up period were censored at that timepoint. Subjects dying of a reason not related to the catheter patency were censored at the time of death.

Table 4. Calculated Rates of Infection Events

Number of Events	Events/1000 Days* (Total Catheter Days†)
CRBSI Events	
4	0.56 (7116)
Local infection events	
2	0.28 (7116)
CRBSI + local infection events	
6	0.84 (7116)

*Calculated as $(n \text{ of infection events}) / (\text{total catheter days} / 1000)$.

†Total catheter days = Σ of n of individual subject's catheter days, from insertion up to 6 months since insertion (183 days; protocol-specified follow-up period) or until termination of subject's participation in the study, whichever occurred first, for each respective subject.

CRBSI, catheter-related bloodstream infection.

instance, the relevant European guidelines still consider blood flow of 300 ml/min an adequate threshold in hemodialysis efficiency assessment, despite providing a definition for catheter dysfunction different from their 2006 American counterparts.^{2,3} Noteworthy, in Europe, BFRs less than 300 ml/min could be used, with longer dialysis treatment durations compensating for any reduction in flow.²⁰ The 2019 update of NKF KDOQI guidelines retracted the strict 300 ml/min requirement, citing misinterpretation of an opinion-based guideline recommendation as an absolute requirement by stakeholders. A more lenient definition of CVC dysfunction was offered instead, namely, failure to maintain the prescribed extracorporeal blood flow required for adequate hemodialysis without lengthening the prescribed hemodialysis treatment.⁶

The primary efficacy result of the Pristine hemodialysis catheter showing that all devices inserted during the study were patent at the 30-day post-implantation mark without intervention aimed to support this patency, is aligned with the current US⁶ and European² vascular access recommendations. In fact, it is also in line with the more stringent 2006 KDOQI guidelines,¹ which viewed 5% as the acceptable rate of primary failure of tunneled CVCs, that is, the proportion of CVCs unable to support blood flow of 300 ml/min within the first week after insertion, despite at least one attempt to improve flow.²¹ The 89.7% patency at 6 months and the mean catheter survival time of 161.69 days achieved with the Pristine hemodialysis catheter in this trial are also promising. In this regard, it is worth mentioning that insertion of the Pristine hemodialysis catheter adhered to the rule of 2 seconds¹⁶ to assure the highest sensitivity for predicting inadequate dialysis, a test of paramount importance especially in non-side-hole catheters, considering their propensity for positional occlusion. As it must take 2 seconds to fill a 20-ml syringe with the plunger fully withdrawn to pass this test, its success represents a 600-ml/min catheter BFR.

With regard to safety of use of the Pristine hemodialysis catheter, in this study, the device presented results comparable to those required from¹ or associated with the tunneled cuffed CVCs.^{22–29} Specifically, the reported CRBSI rate of 0.56 per 1000 catheter days aligns well with the expected 0.6–6.5 episodes per 1000 catheter days.^{30,31} Of note, the updated KDOQI recommendations consider it reasonable that in hemodialysis patients for whom a cuffed, tunneled CVC is the most appropriate permanent dialysis access there is no maximum time limit to CVC use.⁶ As the economic toll of CRBSI treatment is

substantial,³⁰ reducing the number of infections has implications going far beyond the needs of an individual patient.

Finally, as there were no occurrences of safety events not previously described in the peer-reviewed literature reporting data from the state-of-the-art devices, the safety results of this study are well in line with the expectations from a safe CVC, surpassing the current safety recommendations.

Being a single-arm trial, this article is subject to certain limitations inherently imposed by the trial setting.³² Although more rigorous investigation is needed, the results of this trial suggest that the unique side-hole-free design of the Pristine hemodialysis catheter may improve performance and safety in providing vascular access to hemodialysis patients relative to the traditional catheters. This may be due, in part, to the AP orientation of the Y-shaped tip, optimally positioning the arterial lumen in the mid-right atrium and preventing contact of the tip with tissue; and, in part, to the slot in the tip wall, functioning as a pressure relief opening when occlusion starts to form. A larger randomized trial is needed to better assess these observations.

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References

1. Group VAW: Clinical practice guidelines for vascular access. *Am J Kidney Dis* 48(Suppl 1): S248–73, 2006.
2. Schmidli J, Widmer MK, Basile C, et al: Editor's choice - vascular access: 2018 Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS). *Eur J Vasc Endovasc Surg* 55: 757–818, 2018.
3. Tordoir J, Canaud B, Haage P, et al: EBPG on vascular access. *Nephrol Dial Transplant* 22(Suppl 2): ii88–117, 2007.
4. Ravani P, Palmer SC, Oliver MJ, et al: Associations between hemodialysis access type and clinical outcomes: A systematic review. *J Am Soc Nephrol* 24: 465–73, 2013.
5. Grubbs V, Wasse H, Vittinghoff E, Grimes BA, Johansen KL: Health status as a potential mediator of the association between hemodialysis vascular access and mortality. *Nephrol Dial Transplant* 29: 892–898, 2014.
6. Lok CE, Huber TS, Lee T, et al: KDOQI Clinical Practice Guideline for Vascular Access: 2019 Update. *Am J Kid Dis* 75 (4, Suppl 2): S1–S164, 2020.
7. Lok CE: Fistula first initiative: Advantages and pitfalls. *Clin J Am Soc Nephrol* 2: 1043–1053, 2007.
8. United States Renal Data System: 2017 USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States. Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2017.
9. United States Renal Data System: 2019 USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States. Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2019.
10. Noordzij M, Jager KJ, van der Veer SN, et al: Use of vascular access for haemodialysis in Europe: A report from the ERA-EDTA Registry. *Nephrol Dial Transplant* 29: 1956–1964, 2014.
11. Alencar de Pinho N, Coscas R, Metzger M, et al: Vascular access conversion and patient outcome after hemodialysis initiation with a nonfunctional arteriovenous access: A prospective registry-based study. *BMC Nephrol* 18: 74, 2017.
12. Hussein WF, Mohammed H, Browne L, Plant L, Stack AG: Prevalence and correlates of central venous catheter use among haemodialysis patients in the Irish health system - a national study. *BMC Nephrol* 19: 76, 2018.
13. Ash SR: Advances in tunneled central venous catheters for dialysis: Design and performance. *Semin Dial* 21: 504–515, 2008.

14. Moore HL: Side holes at the tip of chronic hemodialysis catheters are harmful. *J Vasc Access* 2: 8–16, 2001.
15. Tal MG, Livne R, Neeman R: Clot accumulation at the tip of hemodialysis catheters in a large animal model [published online ahead of print December 25, 2020]. *J Vasc Access*. doi: 10.1177/1129729820983617.
16. Smith JC, Sullivan KL, Michael B: Postprocedural aspiration test to predict adequacy of dialysis following tunneled catheter placement. *Cardiovasc Intervent Radiol* 29: 576–579, 2006.
17. American College of Radiology: *Practice Guidelines for Percutaneous Management of the Thrombosed or Dysfunctional Dialysis Access*. Reston, VA, American College of Radiology, 2000, pp 473–485.
18. Gray RJ, Sacks D, Martin LG, Trerotola SO; Society of Interventional Radiology Technology Assessment Committee: Reporting standards for percutaneous interventions in dialysis access. *J Vasc Interv Radiol* 14(9 Pt 2): S433–S442, 2003.
19. Sidawy AN, Gray R, Besarab A, et al: Recommended standards for reports dealing with arteriovenous hemodialysis accesses. *J Vasc Surg* 35: 603–10, 2002.
20. Kelber J, Delmez JA, Windus DW: Factors affecting delivery of high-efficiency dialysis using temporary vascular access. *Am J Kidney Dis* 22: 24–29, 1993.
21. Besarab A, Pandey R: Catheter management in hemodialysis patients: Delivering adequate flow. *Clin J Am Soc Nephrol* 6: 227–234, 2011.
22. Jaffer Y, Selby NM, Taal MW, Fluck RJ, McIntyre CW: A meta-analysis of hemodialysis catheter locking solutions in the prevention of catheter-related infection. *Am J Kidney Dis* 51: 233–241, 2008.
23. Miller LM, Clark E, Dipchand C, et al: Hemodialysis tunneled catheter-related infections. *Can J Kidney Health Dis* 3: 2054358116669129, 2016.
24. Moore CL, Besarab A, Ajluni M, et al: Comparative effectiveness of two catheter locking solutions to reduce catheter-related bloodstream infection in hemodialysis patients. *Clin J Am Soc Nephrol* 9: 1232–1239, 2014.
25. Van Der Meersch H, De Bacquer D, Vandecasteele SJ, et al: Hemodialysis catheter design and catheter performance: A randomized controlled trial. *Am J Kidney Dis* 64: 902–908, 2014.
26. Silva TN, Mendes ML, Abrão JM, Caramori JT, Ponce D: Successful prevention of tunneled central catheter infection by antibiotic lock therapy using cefazolin and gentamicin. *Int Urol Nephrol* 45: 1405–1413, 2013.
27. Spector M, Mojibian H, Eliseo D, et al: Clinical outcome of the Tal Palindrome chronic hemodialysis catheter: Single institution experience. *J Vasc Interv Radiol* 19: 1434–1438, 2008.
28. Ye C, Mao Z, Zhang P, et al: A retrospective study of palindrome symmetrical-tip catheters for chronic hemodialysis access in China. *Ren Fail* 37: 941–946, 2015.
29. Wang L, Wei F, Chen H, Sun G, Yu H, Jiang A: A modified de novo insertion technique for catheter replacement in elderly hemodialysis patients: A single clinic retrospective analysis. *J Vasc Access* 17: 506–511, 2016.
30. Lok CE, Mokrzycki MH: Prevention and management of catheter-related infection in hemodialysis patients. *Kidney Int* 79: 587–598, 2011.
31. Ravani P, Gillespie BW, Quinn RR, et al: Temporal risk profile for infectious and noninfectious complications of hemodialysis access. *J Am Soc Nephrol* 24: 1668–1677, 2013.
32. Evans SR: Clinical trial structures. *J Exp Stroke Transl Med* 3: 8–18, 2010.