



Clinical and Regulatory Considerations for Central Venous Catheters for Hemodialysis

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Abstract

Central venous catheters remain a vital option for access for patients receiving maintenance hemodialysis. There are many important and evolving clinical and regulatory considerations for all stakeholders for these devices. Innovation and transparent and comprehensive regulatory review of these devices is essential to stimulate innovation to help promote better outcomes for patients receiving maintenance hemodialysis. A workgroup that included representatives from academia, industry, and the US Food and Drug Administration was convened to identify the major design considerations and clinical and regulatory challenges of central venous catheters for hemodialysis. Our intent is to foster improved understanding of these devices and provide the foundation for strategies to foster innovation of these devices.

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The Kidney Health Initiative

The Kidney Health Initiative (KHI) is a public-private partnership between the American Society of Nephrology (ASN), the US Food and Drug Administration (FDA), academia, industry, and patient groups that aims to advance scientific understanding of kidney health and foster development of therapies for kidney diseases. The KHI project *Regulatory Considerations Affecting Device Approval* project was designed to: (1) describe central venous catheters for hemodialysis (hereafter referred to as CVCs), (2) identify common issues raised during reviews of FDA submissions, (3) identify the major benefits and risk of CVC, (4) discuss recent technological advances for these devices, and (5) enumerate limitations of currently available technology requiring research or device modification. For a full list of workgroup members, see Supplemental Material.

Background: CVCs for Hemodialysis

As of 2014, there were 408,711 patients receiving maintenance hemodialysis (HD) (1). Current options for vascular access in patients receiving HD for ESKD include an arteriovenous fistula (AVF), arteriovenous graft (AVG), or CVC. The percentage of patients using a CVC varies depending on a number of parameters, including time of pre-ESKD care. As of the 2017 US Renal Data System annual data report, 80% of patients with ESKD had a CVC as vascular access whereas 61.9% had neither an AVF or AVG in place at the initiation of HD (2). Among all patients on prevalent HD, 62.9% had an AVF, 17.7% had an AVG, and 19.4% had a CVC as vascular access.

Section 1: CVC Catheter Design and Function

General Comments

There are two classes of marketed CVC: (1) short-term (nontunneled) devices that are generally

without a cuff, tapered, stiff, and usually inserted *via* a guidewire; and (2) long-term (tunneled) devices are blunt, soft-bodied, contain a subcutaneous device for fixation of the catheter, and are designed to be placed through a split-sheath (3). These catheters typically have one lumen for blood outflow (“arterial”) and one for blood return (“venous”). The arterial and venous ports are separated with the arterial port positioned proximal to the venous port to minimize recirculation. Early examples of short-term CVC were the Shaldon (4), Uldall (5), and Mahurkar (6) catheters. Shaldon catheters are twin single-lumen catheters, one for arterial flow one and one for venous flow. Both can be placed into a central vein in staggered position or one can be placed in an artery and one in a vein. Uldall catheters were concentric in design, with arterial blood flow in the outer lumen. The Mahurkar catheter was the first to implement the “DD” (Double-D) design, with arterial and venous lumens separated by a flat wall. The distal portion of the arterial lumen was blocked by a solid plug. Currently, almost all CVC are dual-lumen and use the DD design of the internal lumen of the catheter because this design offers relatively low hydraulic resistance and small overall diameter (7). Simplistic drawings of these three catheters are shown in Figure 1.

There have been six different tip designs for long-term CVC over the years (Figure 2). The Quinton device was an oval single-body catheter of 20 French circumference, with round blood lumens. It was the first CVC to contain a subcutaneous polyester cuff to fix the catheter position and prevent bacterial migration past the cuff (8). Mahurkar applied the DD design to a long-term catheter, and this provided adequate blood flow through a 15 French catheter (9). Canaud developed twin cylindrical catheters that were placed

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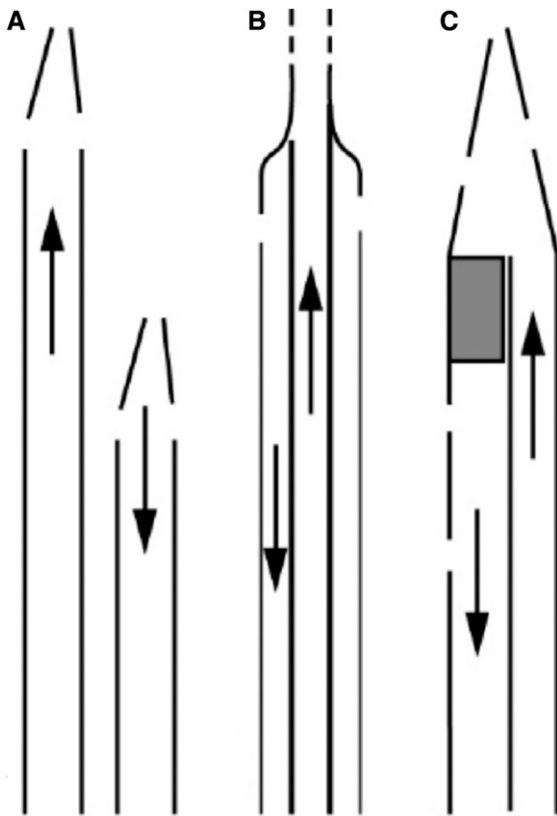


Figure 1. | Comparison of overall design of various CVC for acute hemodialysis shows direction of flow and side hole location. Spaces indicate side holes. (A) Shaldon catheters. (B) Uldall concentric catheter. (C) Mahurkar DD catheter.

in staggered position within the superior vena cava or right atrium. A subcutaneous solid block secured the catheter. Tesio replaced the block with polyester cuffs (10). Ash developed the split-tip catheter, in which the DD body separates into two separate tips. This allowed entry holes on all sides of each distal lumen (11–13). Tal developed the symmetrical catheter in which both lumens end in a tapered end with a side hole (14–17). The self-centering catheter developed by Ash had tips facing inward away from vein and atrium walls. Small pressure-relief holes are placed on the inside surfaces near the tips (18–20).

General Features of Short-Term and Long-Term CVCs

Short-Term (Nontunneled) CVCs

Short-term CVCs made of polyurethane are comparatively stiff; however, this material becomes less rigid after placement when it reaches body temperature (21,22). The stiffness of short-term CVCs creates some difficulties in adapting them to the curves of the veins and body. Catheters placed in the right internal jugular (IJ) vein have a fairly straight course into the superior vena cava (SVC). However, left-sided IJ catheters must make two or three bends to reach the SVC, and they must be reasonably soft to conform to this route and avoid excess pressure on the brachiocephalic vein and superior vena cava. The external portion of short-term CVCs may be either straight or precurved to allow the external portion to bend over

the clavicle and to lie on the anterior chest. Precurved catheters are associated with a reduced likelihood of kinking and are more comfortable for patients than straight catheters. A historic analysis of change in catheter type used at the Vrije Universiteit Medical Center (Amsterdam, The Netherlands) showed that there was a lower rate of removal (15% versus 53%) and bacteremia (0 versus 5.6 per 1000 catheter days) in 65 precurved versus 104 straight CVCs (23). Blood flow rates are generally lower in short- versus long-term CVCs because of a smaller lumen size, but flows are generally adequate to provide the desired clearance for AKI (21).

Long-Term (Tunneled) CVCs

Unlike short-term CVCs, long-term CVCs require softer materials such as polyurethane/polycarbonate copolymer or silicone to enhance longevity within the vessel and reduce the risk of vascular damage (24). All current long-term catheters now include a polyester felt cuff in the subcutaneous tract. The purpose of the cuff is to fix the catheter in position and to provide a physical barrier against infection once fibrous tissue incorporates into the cuff. Long-term CVCs generally provide higher blood flow rates and more efficient solute clearance than short-term CVCs (21,25). Both types of catheter utilize DD lumens, which provide the lowest surface-to-volume ratio (21). The lumens are somewhat larger in the long-term CVC, however, providing blood flow rates of up to 400 ml/min or more. Essentially all long-term CVCs have additional side holes to maintain blood flow when the end holes are covered by thrombus or fibrin sheath.

Lumen and Tip Design of Long-Term CVCs

As described above, tips of single-body catheters may be step-tip, split-tip, or symmetric-tip. In step-tip or split-tip catheters, their end lumens are separated by 3–4 cm to create a “proximal” arterial intake and “distal” venous outflow. This is done to diminish recirculation of blood from the venous tip to the arterial of the catheter; however, in the forward-flow mode, recirculation in clinical use averages about 7%. In reverse-flow mode, recirculation for split-tip and step-tip CVCs can increase to 10%–30% of blood flow (26). The symmetric-tip CVC has a slanted-tip design that diminishes recirculation by a different mechanism from the other catheters. Kinetic energy of the venous blood propels it downstream from the catheter. The arterial blood is removed through the upstream part of the sloped tip and through a side hole. *In vitro* studies demonstrate no venous-to-arterial recirculation regardless of whether the catheter is operated in the forward or backward directions (26,27). Another advantage of the symmetrical catheter is that if one port is positioned within the right atrium then both tips should reside there. This tip position is important to CVC function because it may diminish fibrous sheathing of the catheter tip. In clinical use, however, there does not appear to be a significant decrease in recirculation percentage between the symmetrical catheter and the split-tip and step-tip catheters when the latter are run in the usual forward direction (16,26).

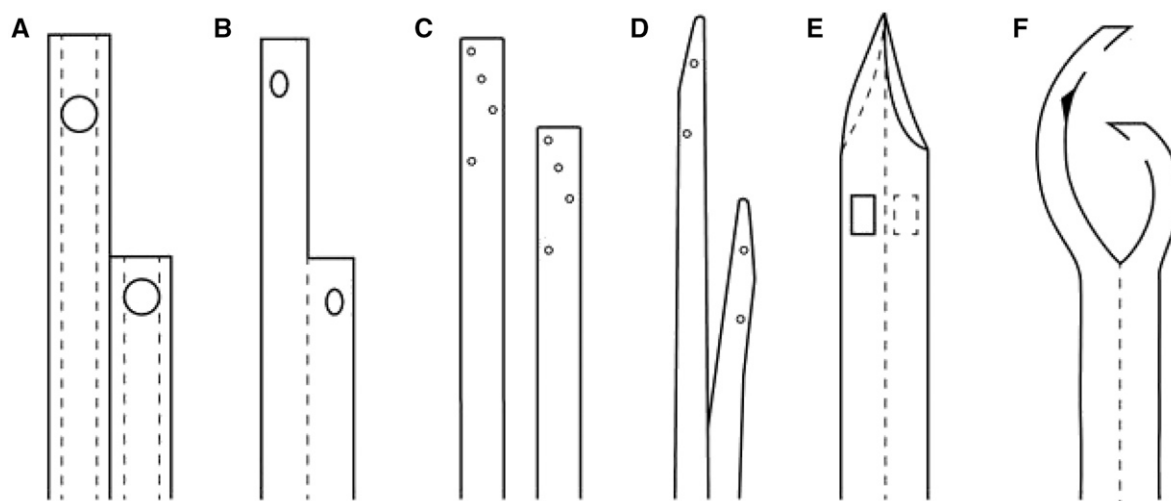


Figure 2. | Comparison of the overall design of various CVC for maintenance hemodialysis, with axial cross-section of the catheters shows the locations of side holes and ports. Circles, squares, and spaces indicate side holes or ports. (A) Quinton PermCath (20 French oval cross-section). (B) Mahurkar catheter, single body, DD design. (C) Canaud and Tesio twin catheters. (D) Ash split-tip catheter. (E) Symmetric-tip catheter by Tal. (F) Self-centering catheter (arrowhead indicates position of a self-sealing hole to allow the catheter to be threaded over a single guide-wire or stylet).

Split-tip CVCs demonstrate somewhat longer patency in comparison with step-tip CVCs but provide no greater blood flow rate initially (13,28). Two recent, randomized, controlled studies demonstrated greater catheter patency of the symmetric-tip CVC along with lower dysfunction rates in comparison to the step-tip CVC (16,17). Other symmetric-tip CVCs have been introduced into the market with distal lumens that are angled and on opposing sides of the catheter so that blood exiting the venous port is deflected away from blood entering the arterial port of the catheter. This latter design may reduce platelet activation during the high-flow conditions of dialysis (27,29) and potentially result in longer catheter patency from significantly lower rates of thrombosis (30).

The self-centering catheter is designed to prolong CVC survival by preventing the end holes from coming into direct contact with the vessel wall, which can lead to fibrin sheath formation and encasement of the end holes and vascular injury. Several prospective clinical trials have indicated a high patency of the self-centering catheter, with approximately 90% patency after 3 months of use (20,31,32). This patency compares favorably to numerous studies of other catheters (32). Although one of these trials was multicenter, none were prospectively controlled.

Section 2: Benefits and Risks of CVCs

It is important to consider the benefits and risks of CVCs, which are displayed in Table 1. A few major risks (complications), including fibrous sheathing, central venous stenosis (CVS), and infection, are discussed in greater detail below.

CVS and Fibrous Sheathing

Many factors contribute to development of CVS in patients with a CVC, including position of the catheter in the vessel, turbulent flow, inflammation, longer dialysis vintage, and multiple CVC insertions (33–35). Histologically,

there is hyperplasia of endothelial cells, fibrous tissue, and thrombosis (36). Long-term sequelae include loss of future venous access, increased number of catheter-related infections, and earlier catheter removal (37).

Fibrin sheaths are very common, although the clinical implications vary. Fibrous sheathing may cause thrombus formation and disturbances in blood flow (38). The mechanism for loss of blood flow involves reduction of the space surrounding the arterial tip of the catheter, inducing an increase in flow velocity and negative pressure, thus increasing the risk of venous collapse and likelihood of pulling the vein wall over the tip (18,39).

Endothelial damage and fibrin sheath formation probably begin to occur within days of placement, at catheter points of contact with the vein wall (39,40). Fibrin sheath has been demonstrated in 47% of long-term CVCs at time of removal (41). Loss of flow in the catheter occurs when the fibrin sheath reaches the tip of the catheter.

The relationship between fibrin sheathing and CVS is not clear. Although many dialysis patients develop radiographic signs of CVS, the majority remain asymptomatic. In one study of 202 patients, 64% had radiographic evidence of CVS whereas only 9% had symptoms or signs such as dilated and torturous veins (42). CVCs placed in the right IJ vein had lower rates of CVS than those placed in the subclavian vein (43), a major factor that has contributed to avoidance of catheter placement in subclavian vessels. Nevertheless, CVS rates remain as high as 40%–50% (35,37,44–47). Long-term sequelae include loss of future venous access, increased number of catheter-related infections, and earlier catheter removal (47). Central stenosis may severely limit use of the arms for graft or fistula access (48). Central stenosis from placement of femoral catheters can also limit using the iliac vein during kidney transplantation.

One study in pigs demonstrated that standard cylindrical silicone catheters caused marked stenosis and occlusion of the SVC within weeks of placement (19). However, if the tip

Table 1. Major benefits and risks associated with the use of central venous catheters

Benefits	Risks
High likelihood of successful insertion Does not require venipuncture Can be inserted into multiple sites Allows for maturation of fistula or graft Bridging dialysis Allows measurement of hemodynamic variables Can be used immediately after insertion Ability to be used for months to few years Ease of use and painless access Absence of cardiopulmonary recirculation Relative ease of managing thrombotic complications Availability of catheter repair without need for exchange Low cost of placement and exchange	Insertion risks Hemothorax Pneumothorax Air embolism Arrhythmia Pericardial tamponade Atrial and venous perforation Dissection/occlusion Use risks Luminal thrombosis (8,38) Infection (84–88) Poor function/unreliable blood flows Limited functional longevity (38,84) Inflammation Increased rate of hospitalization (89–92) Increased risk of death (93–95) Increased cost (70,94) Central venous stenosis/stricture Vascular ingrowth Fibrin sheath formation Fibrin tail or flap formation Patient cosmetic concern
Most complications (risks) of catheter placement are apparent shortly after catheter placement. Complications seen during use of the catheter can occur any time after placement.	

of the catheter was supported by a silicone ring, damage to the SVC was minimized. Thus, support of a catheter by a few points of contact with the wall of the SVC or atrium may help to prevent fibrin sheathing and central stenosis (18).

Infection

Although the rate of catheter-related bloodstream infections (CRBSIs) is highest with short-term CVCs (8,49–52), the rate remains high for long-term CVCs. The risk of developing a CRBSI is higher among patients with a long-term CVCs, with rates similar to those found in neonatal intensive care units (ICUs), although only about 50% as high as seen in adult ICU settings (51). Among 73 hospitals in England between 1997 and 2001, the incidence rate of CRBSI among patients using a long-term CVC was 21 incidents per 1000 patient-days at risk (53). A Canadian survey found that patients with a long-term CVC had the greatest risk of developing a CRBSI among all hospitalized patients (54). Marr *et al.* (55) studied rates of CRBSI in 102 patients (16,801 catheter days) with long-term CVCs. They found that 40% of patients developed bacteremia, with a rate of 3.9 episodes per 1000 catheter days.

The organisms most commonly seen in CRBSIs in long-term CVCs are *Staphylococcus (Staph) aureus* and coagulase-negative *Staph* (55,56). Several other studies (55,57–68) show that the most common other organisms causing CRBSI in short- or long-term CVC are *Enterococcus faecalis*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Enterobacter cloacae*, *Pseudomonas aeruginosa*, and *Escherichia coli*.

The outcome of CRBSI in patients with a CVC is often serious. For example, Siegman-Igra *et al.* (52) found that among patients who developed bacteremia, 17% died. Maraj *et al.* (69) found that 1.4% patients receiving dialysis with a long-term CVC developed infective endocarditis,

resulting in a 1-year mortality rate of 56.3%. Other complications of CRBSI include osteomyelitis, septic arthritis, and epidural abscess (9).

Section 3: Review Deficiencies

The FDA uses the FDA guidance documents (which are distributed for public comment before finalization), published and accepted standards, and literature as its major references for reviewers of studies or marketing applications. These resources are not binding but merely serve to provide a framework. Although FDA does not share confidential information, information provided in previous applications helps maintain similar requirements for all manufacturers and investigators for a specific product type.

Tables 2 and 3 exhibit various common concerns (commonly called “deficiencies”) raised by the FDA during review of premarket submissions, including investigational device exemption and 510(k) (premarket notification) submissions. These lists are not product specific (*i.e.*, for any particular company) or fully comprehensive, but are displayed here to highlight common examples of issues that arise during review of submissions to the agency.

Quantitative Time-Kill Assay

A common question posed by innovators and investigators is the preferred method to study the efficacy of antimicrobial agents for CVC. One method for performing time-kill assay involves preconditioning the catheter (or segments) to simulated clinical conditions, such as immersion in serum and flushing fluids through lumens, in a manner that simulates the use of the device in a clinical setting for the maximum claimed use time, and then exposing the device to a liquid suspension of

Table 2. Common concerns, with applicable resources and references, raised by the FDA during review of premarket submissions for uncoated catheters

Category	Main Issues of FDA Concern Missing or Insufficient in Submissions	Reference for Deficiencies
Device description	Description of catheter accessories not clear Inconsistency in catheter materials Lack of colorant information provided Inadequate diagrams of proposed or predicate devices	FDA 1997 GD: Sections D-1 and D-4d (96)
Predicate device comparison	Materials (including colorants) different from predicate catheters	FDA 1997 GD: Sections III and E-3 (96) FDA 2016 GD: Section 4 (97)
Labeling	Incomplete or missing lists of warnings and complications Missing list of contraindications Incomplete cleaning/chemical compatibility Incomplete instructions on proper positioning	FDA 1997 GD: Sections B-1 and B-3-k (96) FDA 2016 GD: Section IV.F (97)
Sterilization/shelf life	Incomplete instructions on ways to reduce catheter-related bloodstream infections Lack of real-time aging validation or concern about design changes on aging Internal standards not in agreement with industry standard Lack of comparison of packaging materials and configuration for proposed and predicate devices Inconsistent shelf life with past version of device	FDA 1997 GD: Sections F-5-b Attachment 2 (96) FDA 2016 GD: Section IV.E (97) Predicate reviews and requirements Industry standards
Biocompatibility	Incomplete test methods and reports Extraction procedure inadequately described	FDA 1997 GD: Section F-1 (96) Other guidance and International Organization for Standardization standards cited FDA 2016 GD: Section IV.C (97)
Performance testing	Inadequate systemic toxicity testing Inadequate thrombosis study results Inadequate toxicology risk assessment Materials incompletely characterized Performance testing did not support reversibility Incomplete clamp test methods and results Incomplete mechanical hemolysis test results Air/leak testing result inadequate Flow rate testing: proper solvent Inadequate tensile test results with reduced performance after accelerated aging Inadequate pressure versus flow-testing methodology Lack of acceptance criteria for recirculation testing Inadequate chemical tolerance or exposure test results Differences in MRI compatibility between proposed and predicate devices	FDA 2016 GD: Section IV.G.2 (97)

FDA, US Food and Drug Administration; GD, Guidance Document; MRI, magnetic resonance imaging.

microorganisms (inoculum) and monitoring the number of viable microorganisms attached to the antimicrobial (test) catheter. The antimicrobial catheter is tested side-by-side with a control catheter of identical composition that does not contain antimicrobial agents (positive control). Ideally, the test will also include a negative control that is exposed to the suspending liquid without microorganisms (70).

Clinical testing of CVCs depends on the claims being sought and the type of materials added to the catheters, the known risks of the catheter, and the level of regulatory control needed to mitigate those risks. For example, adding a

new coating to a catheter, such as a drug not previously evaluated by the FDA, could affect the regulatory pathway (*i.e.*, 510(k) versus premarket approval).

Section 4: Technological Advances that May Require Special Consideration by the FDA in Future Study/Marketing Applications **Antimicrobial-Coated or Impregnated CVCs in the General Population**

There is a relative scarcity of information about antimicrobial-coated or impregnated CVCs in the HD population and

Table 3. Common concerns, with applicable resources and references, raised by the US Food and Drug Administration (FDA) during review of premarket submissions for catheters with additives, coatings, impregnations, or bondings

Category	Main Issues of FDA Concern Missing or Insufficient in Submissions
Performance testing considerations	<p><i>In vitro</i> test methods to assess pathogen killing: quantitative time-kill assays (<i>i.e.</i>, log reduction of the challenge organism) measure the amount of organism killed. Consideration should be given to calculation of the log reduction of any additive or coating relative to the uncoated control. For the uncoated control method, the following could be considered:</p> <p>Assay conditions that simulate, as closely as possible, actual use</p> <p>Clinically relevant pathogens</p> <p>Results on the fully finished catheter</p>

in these CVCs for infusion in the general population. Gastmeier and Geffers (71) studied 33 randomized, controlled trials and ten meta-analyses and found that the use of impregnated or coated catheters resulted in a 29%–95% reduction of CRBSI. Gilbert and Harden (72) assessed seven randomized, controlled trial involving impregnated CVCs for the prevention of CRBSI and found that use of heparin-coated or antibiotic-impregnated CVCs resulted in a significant reduction in CRBSI. Various single-center studies of patients with a variety of conditions other than HD support the efficacy of the coating or impregnation of CVCs to reduce the incidence of CRBSI. In one randomized, double-blind study, Raad *et al.* (73) showed that short-term CVCs coated with minocycline and rifampin reduces the risk for colonization and CRBSI. Darouiche *et al.* (74) showed that short-term catheters impregnated with minocycline-rifampin have a lower incidence of infection than catheters impregnated with chlorhexidine-silver. However, the minocycline-rifampin-impregnated catheters were impregnated on both the extraluminal and intraluminal surfaces whereas the chlorhexidine-silver sulfadiazine-impregnated catheters were only coated on the extraluminal surface. There have been several prospective, randomized studies showing that short-term CVCs impregnated with chlorhexidine-silver sulfadiazine have a lower incidence of CRBSI (75–77). One meta-analysis of antimicrobial-coated CVCs in the ICU showed no significant clinical benefit for reduction of CRBSIs or other patient outcomes (78). Antibacterial resistance to antibiotic impregnated or coated catheters has not been demonstrated in several clinical studies (73,74).

Antimicrobial-Coated or Impregnated CVCs for HD

The true efficacy of antimicrobial-coated or impregnated CVCs to reduce infection is uncertain because of various methodological limitations, variable definitions (*e.g.*, infection), inconsistent end points, and inadequate statistical analyses. One randomized, controlled trial with 77 patients with short-term CVCs showed a reduction in colonization

with bismuth coating, although there was no effect on time-to-catheter removal (79). Antiseptic and antibiotic catheter lock solutions have been instilled into CVCs for infusion, but catheter lock solutions are mainly regulated as drugs and a discussion of their use is beyond the scope of this project.

Extrapolation of data for antimicrobial-coated or impregnated CVCs in patients receiving intensive care may be limited by the differences in the non-HD and HD populations. However, the results of randomized, controlled trials in the acute care population do suggest the potential for a reduction of CRBSI with an antimicrobial-coated or impregnated CVC.

Catheter Coatings

Within the HD population, there are few large studies assessing the efficacy and safety of impregnated or coated catheters for the prevention of CRBSI. Rabindranath *et al.* (80) conducted a systematic review of trials of long-term CVCs impregnated or coated with antimicrobial products and found that use of exit-site antimicrobials may reduce the incidence of CRBSI, whereas antimicrobial impregnated catheters and perioperative systemic antimicrobial administration are not beneficial. Similarly, Trerotola *et al.* (81) showed that use of silver-coated long-term CVCs did not reduce colonization and infection rates versus uncoated CVCs. Bambauer *et al.* (82) showed that silver-coated long-term CVCs have lower (11% versus 44%) colonization rates compared with uncoated CVCs. Finally, Jain *et al.* (83) studied the effect of heparin-coating in a controlled study of 175 long-term CVCs and found that CRBSI were less frequent in patients with heparin-coated CVCs versus uncoated CVCs, whereas catheter survival was similar in the two groups. Generally, in these studies and in products on the market, the antibacterial coatings are only on the outside of the catheter and in the portion contacting the subcutaneous tunnel (81–83).

Summary

CVCs for HD are necessary for a subset of patients with ESKD. It is our hope that improved understanding of the regulatory requirements for marketing of devices will help foster device iteration and innovation and result in more effective and safe devices for patients.

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Disclosures

S.T. is a consultant for MedComp, Teleflex, B Braun, Bard Peripheral Vascular, Cook Royalties-Cook, and Teleflex. T.C. receives royalties from, and has a consulting agreement with Arrow-Teleflex, and is a consultant for C.R. Bard. S.A. is also a consultant with C.R. Bard.

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Supplemental Material

APPENDIX I: Members of the Kidney Health Initiative “Regulatory Policies and Positions Affecting Device Approval in the US: Tools to Assess the Process and Foster Device Development for Patients with Kidney Disease” Workgroup’s Central Venous Catheter Subgroup

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