Vascular Access for Hemodialysis Patients
New Data Should Guide Decision Making

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Abstract
This commentary critically examines key assumptions and recommendations in the 2006 Kidney Disease Outcomes Quality Initiative vascular access guidelines, and argues that several are not relevant to the contemporary United States hemodialysis population. First, the guidelines prefer arteriovenous fistulas (AVFs) over arteriovenous grafts (AVGs), on the basis of their superior secondary survival and lower frequency of interventions and infections. However, intent-to-treat analyses that incorporate the higher primary failure of AVFs, demonstrate equivalent secondary survival of both access types. Moreover, the lower rate of AVF versus AVG infections is counterbalanced by the higher rate of catheter-related bloodstream infections before AVF maturation. In addition, AVFs with assisted maturation (interventions before successful AVF use), which account for about 50% of new AVFs, are associated with inferior secondary patency compared with AVGs without intervention before successful use. Second, the guidelines posit lower access management costs for AVFs than AVGs. However, in patients who undergo AVF or AVG placement after starting dialysis with a central venous catheter (CVC), the overall cost of access management is actually higher in patients receiving an AVF. Third, the guidelines prefer forearm over upper arm AVFs. However, published data demonstrate superior maturation of upper arm versus forearm AVFs, likely explaining the progressive increase in upper arm AVFs in the United States. Fourth, AVFs are thought to fail primarily because of aggressive juxta-anastomotic stenosis. However, recent evidence suggests that many AVFs mature despite neointimal hyperplasia, and that suboptimal arterial vasodilation may be an equally important contributor to AVF nonmaturation. Finally, CVC use is believed to result in excess mortality in patients on hemodialysis. However, recent data suggest that CVC use is simply a surrogate marker of sicker patients who are more likely to die, rather than being a mediator of mortality.
Canada, of 1012 new AVFs and 128 new AVGs documented primary failure rates of 40% and 19%, respectively (10). Both studies confirmed that secondary AVF survival was indeed superior to that of AVGs (5 versus 2 years), when the analysis was restricted to accesses successfully used for dialysis. However, in an intent-to-treat analysis that included all vascular accesses (including those with a primary failure), secondary access survival was equivalent for AVFs and AVGs (Figure 1). In fact, AVG survival was superior to that of AVFs during the first 2 years after access placement. Several smaller observational studies have arrived at similar conclusions (11–13). Thus, among elderly patients with a high comorbidity, whose median life expectancy is about 2 years, AVGs may actually be the preferred choice. In contrast, AVF maturation with a shorter secondary survival and more frequent interventions after maturation, compared with those with unassisted AVF maturation (16). Finally, a recent analysis of a national cohort of elderly patients on hemodialysis reported that the median time from access placement to its successful use (assisted survival) was 1.8- and 4.6-fold higher if the AVF required one or two or more interventions to assist maturation. An accompanying editorial (19) commented that, “Although usability for dialysis is often considered an indicator of successful maturation, how the fistula got there (i.e., how it became usable) seems to be important.” A second study of 289 patients with a new AVF observed a two-fold higher likelihood of abandonment among AVFs with assisted maturation versus unassisted maturation (16). Remarkably, AVFs with assisted maturation had a secondary patency after maturation that was inferior to that of AVGs with unassisted maturation (16) (Figure 2). It is unclear whether the association of assisted maturation with inferior long-term AVF outcomes is a consequence of the intervention itself or simply a reflection of the use of poor-quality vessels that lead to impaired maturation and the need for adjuvant interventions.

The time from access placement to its first successful use for dialysis is substantially longer for AVFs compared with AVGs. The Dialysis Outcomes and Practice Patterns Study reported that only 2% of AVFs, but 78% of AVGs, were used for dialysis in the United States within 1 month of their placement (20). A subsequent publication found that the median time to first successful access cannulation in the United States was 82 days for AVFs and 29 days for AVGs (21). A recent US Renal Data System (USRDS) analysis of patients undergoing access surgery after dialysis initiation observed that 70% of those receiving an AVF remained CVC-dependent after 3 months, compared with 40% of those with an AVG (22). The time to successful cannulation is further prolonged if the AVF requires assisted maturation. For example, a large, single-center study observed a median interval from AVF creation to successful cannulation of 99 days for AVFs with unassisted maturation, compared with 159 days for those with assisted maturation (16). Analysis of a national cohort of elderly patients on hemodialysis reported that the median time from access placement to its successful use was 1 month for AVGs without prior intervention, 2 months for AVGs with a prior intervention, 3 months for AVFs with unassisted maturation, and 4 months for AVFs with assisted maturation (17). Among patients with vascular access placement after initiation of dialysis, such delays in successful AVF use translate into prolonged CVC dependence, with its

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AVF, arteriovenous fistula; AVG, arteriovenous graft; CVC, central venous catheter.
associated risk of CVC-related bloodstream infections. In one observational study, the duration of CVC dependence until successful access use was 4 months for AVFs versus 1 month for AVGs. The proportion of patients experiencing a catheter-related bloodstream infection before access use was 44% and 24%, respectively (9). After successful access use, the annual rate of access infection was 9.7% for AVGs and 0.7% for AVFs. In other words, placement of an AVF rather than AVG entailed a trade-off between early CVC infections and late AVG infections. CVCs are also associated with a 7% risk of central vein stenosis (23), and ipsilateral CVCs have been associated with decreased secondary AVF survival (24).

AVFs Are Cheaper Than AVGs

The 2006 KDOQI vascular access guidelines state that the "costs of implantation and access maintenance are lowest for AVFs" (2). This is certainly true when the analysis is restricted to endovascular and surgical procedures required to maintain access patency after successful use (angioplasty, thrombectomy, or surgical revision). In this regard, numerous publications have reported that AVGs require a three- to seven-fold greater frequency of such interventions than AVFs (15), which would predictably translate into a higher cost for AVG maintenance. A Canadian study compared the overall cost of access management in new patients on dialysis, including 157 who received an AVF and 33 who underwent

Figure 1. Secondary survival of AVFs is superior to that of AVGs when primary failures are excluded, but similar when they are included. Reprinted from reference 10, with permission.
AVG surgery between 1999 and 2001 (25). The access was placed pre-ESKD in 32% of the patients. The overall median cost of access management in the first year after dialysis initiation was lower in patients receiving an AVF versus an AVG (CAN$4641 versus $8152). Remarkably, patients who dialyzed exclusively with a CVC had the lowest annual cost at CAN$3812, likely reflecting the low frequency of catheter-related bloodstream infections. When the costs were calculated per patient-year at risk, they were highest with AVGs, intermediate with CVCs, and lowest with AVFs. The costs reported in this Canadian study may not reflect contemporary costs in the United States because of differences in vascular access practice patterns over time and among countries, selection criteria for access type, the inclusion of patients with pre-ESKD access surgery, and the short patient follow-up time. It is also possible that interventions to promote AVF maturation are more likely if dialysis has already been started, because there is more pressure to accelerate AVF use.

The cost calculation of vascular access management differs when one focuses exclusively on patients who initiate dialysis with a CVC, and subsequently undergo placement of an AVF or AVG, i.e., an intent-to-treat analysis. In that case, the cost includes not just procedures utilized to maintain access patency after its successful use, but also procedures required before successful access use, CVC exchanges due to dysfunction or infection, surgery to place a second access if the initial AVF failed. Unlike the study by Manns et al. (25), the median overall cost of access management in patients dialyzing exclusively with CVCs was far higher, at $28,709 annually, largely driven by hospitalizations for treatment of catheter-related bloodstream infections.

**Forearm AVFs Are Better Than Upper Arm AVFs**

The 2006 KDOQI vascular access guidelines recommend that “the surgeon should focus on sites distally on the extremity, reserving proximal sites for potential future access insertions should the initial access site fail” (2). This recommendation fails to consider the inferior maturation of forearm AVFs relative to upper arm AVFs, particularly among women and older patients, observed when forearm AVFs were commonly placed (28). This disparity persisted even after adoption of routine preoperative vascular mapping to ensure selection of appropriately sized vessels (29). Of note, the age and sex disparities in AVF maturation were worse for AVGs with prior interventions than for AVGs without prior interventions (27,28,29). In the multicenter Dialysis Access Consortium study, AVF thrombosis within 6 weeks of its creation in the control arm was observed in 25% of forearm AVFs versus 13% of upper arm AVFs, and AVF nonmaturation within 6 months in 64 versus 53%,
respec-trately (7). Recognition of the higher maturation of upper arm AVFs has led to a progressive shift from forearm to upper arm AVFs in the United States. Remarkably, over the past 20 years, the proportion of new AVFs placed in the upper arm has increased from 30% to 68% (21). It appears that nephrologists and surgeons in the United States have recognized the inferior outcomes of forearm AVFs in certain patient subsets and modified their practice patterns accordingly, in an attempt to minimize AVF nonmaturation. These efforts have been successful, such that AVF nonmaturation has decreased from approximately 60% observed in the Dialysis Access Consortium trial (2003–2007) (7) down to about 30%–35% obtained more recently in the Hemodialysis Fistula Maturation Study (2010–2013) (8) and the Dialysis Outcomes and Practice Patterns Study 4 (2009–2015) (21). Despite the marked decrease in the proportion of AVFs created in the forearm, indicating a high selection bias, AVF nonmaturation remains higher for forearm than upper arm AVFs (44% versus 33%) (21).

AVFs Fail to Mature Because of Aggressive Neointimal Hyperplasia

An understanding of the pathophysiology of AVF nonmaturation is critical to improving AVF maturation. Nonmaturing AVFs are frequently found to have an underlying juxta-anastomotic stenosis during imaging studies, such as a postoperative ultrasound or angiogram (30,31). In experimental models, AVFs routinely develop flow-limiting juxta-anastomotic stenosis, and the histology reveals severe neointimal hyperplasia (32,33). This observation has led to the hypothesis that aggressive neointimal hyperplasia results in focal stenosis, which in turn impairs AVF maturation. In support of this hypothesis, severe focal intimal hyperplasia was reported in four patients who underwent surgical revision of a nonmaturing AVF (34). A subsequent study described six patients in whom the native vein had minimal intimal hyperplasia, but the draining vein of the nonmaturing AVF (obtained at the time of surgical revision) exhibited severe neointimal hyperplasia (35). Taken together, these two small reports suggested a central role of neointimal hyperplasia in the pathogenesis of AVF stenosis and nonmaturation. Subsequently, a much larger study obtained draining vein samples during the second-stage transposition from 79 patients with planned two-stage AVFs (36). After excluding nonmaturing AVFs, it found no correlation between the magnitude of neointimal hyperplasia and early AVF failure, suggesting that neointimal hyperplasia was necessary, but not sufficient, for AVF nonmaturation. It is unknown, however, whether the timing of neointimal hyperplasia affects AVF maturation, i.e., whether early inward remodeling is more deleterious than later remodeling. Analysis of a large prospective cohort of patients receiving a new AVF in the Hemodialysis Fistula Maturation Study found that preexisting arterial reactivity, assessed by brachial artery nitroglycerin-mediated dilation or flow-mediated dilation, was positively correlated with the 6-week AVF diameter and blood flow (37). This observation suggested that the ability of the artery to dilate after AVF creation was an important determinant of AVF maturation. Collectively, these observations suggest that AVF maturation depends on the relative balance between neointimal hyperplasia (inward remodeling) and sustained vasodilation (outward remodeling) (38). AVF nonmaturation would occur primarily in the subset of patients with both aggressive neointimal hyperplasia and impaired vasodilation (Figure 4).

CVCs Are a Major Cause of Death in Patients on Hemodialysis

Numerous observational studies have reported worse survival in patients dialyzing with a CVC compared with those with an AVF or AVG (39–42). Moreover, patients switching from a CVC to an AVF/AVG have better
survival than those who continue to dialyze with a CVC (39,40). Unfortunately, all of these studies had a huge selection bias that could not be overcome even with sophisticated statistical adjustment for comorbidities or propensity score adjustment. Patients dialyzing with a CVC are inherently sicker than those dialyzing with an AVF or AVG. Similarly, patients who continue to dialyze with a CVC are inherently sicker than those who convert to an AVF (43,44).

The challenge in comparing patient survival between patients who do or do not undergo AVF creation, is that there are important differences not easily captured in administrative databases. If a patient with advanced CKD is perceived by the nephrologist or surgeon to have a reasonable life span, it is likely that an AVF will be placed promptly. In contrast, if the patient has a poor functional status or limited life expectancy, the physician is more likely to postpone AVF creation until after the patient starts hemodialysis. Older patients are less likely to receive an AVF before initiation of dialysis. Older patients also have a higher likelihood of dying after initiating dialysis. Thus, the association between starting hemodialysis with a CVC and dying is confounded by their age. Similarly, a high comorbidity or poor functional status confound the association between CVC use and patient mortality.

Brown et al. (45) addressed this vexing statistical dilemma by designing an innovative approach. They used the USRDS database to compare the survival of three groups of elderly patients on hemodialysis: those who started hemodialysis with an AVF, those who started hemodialysis with a CVC without pre-ESKD AVF surgery, and those who started hemodialysis with a CVC after undergoing pre-ESKD AVF surgery (even if the AVF failed to mature). As expected, patients starting hemodialysis with a CVC without pre-ESKD AVF surgery had worse survival than those starting hemodialysis with an AVF. However, the group initiating hemodialysis with a CVC after an unsuccessful attempt at AVF creation had a patient survival that was more similar to those who initiated dialysis with an AVF (Figure 5). In other words, simply being selected for pre-ESKD AVF surgery was a surrogate marker for a healthier patient with a superior life expectancy.

Quinn et al. (46) evaluated cause-specific mortality in two cohorts of Canadian patients on hemodialysis dialyzing with a CVC, those with and without pre-ESKD AVF creation. In agreement with the study by Brown et al., they observed a greater mortality in the group which underwent attempted AVF placement before dialysis initiation. However, only 2.3% of deaths were adjudicated to be CVC-related. A subsequent mediational analysis by the same investigators found that patients dialyzing with a CVC were more likely to develop an access complication and to die, compared with those dialyzing with an AVF or...
AVG (47). However, the excess deaths in the CVC cohort could not be attributed to the excess in CVC complications.

In conclusion, since publication of the 2016 KDOQI vascular access guidelines, substantial new data has been published. This new information should be incorporated to reinforce current decision making about vascular access.

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References

Figure 5. Patient survival after initiation of hemodialysis with a CVC is higher in those with versus without attempted pre-ESKD AVF creation. Group 1, patients who initiated dialysis with an AVF; group 2, patients who initiated dialysis with a CVC after undergoing pre-ESKD AVF surgery (even if the AVF failed to mature); group 3, patients who initiated dialysis with a CVC without pre-ESKD AVF creation. Patient survival in group 2 was much more similar to that of group 1 than group 3. Reprinted from reference 45, with permission.