

# Dialysis Fistula or Graft: The Role for Randomized Clinical Trials

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The Fistula First Initiative has strongly encouraged nephrologists, vascular access surgeons, and dialysis units in the United States to make valiant efforts to increase fistula use in the hemodialysis population. Unfortunately, the rigid “fistula first” recommendations are not based on solid, current, evidence-based data and may be harmful to some hemodialysis patients by subjecting them to prolonged catheter dependence with its attendant risks of bacteremia and central vein stenosis. Once they are successfully cannulated for dialysis, fistulas last longer than grafts and require fewer interventions to maintain long-term patency for dialysis. However, fistulas have a much higher primary failure rate than grafts, require more interventions to achieve maturation, and entail longer catheter dependence, thereby leading to more catheter-related complications. Given the tradeoffs between fistulas and grafts, there is equipoise about their relative merits in patients with moderate to high risk of fistula nonmaturation. The time is right for definitive, large, multicenter randomized clinical trials to compare fistulas and grafts in various subsets of chronic kidney disease patients. Until the results of such clinical trials are known, the optimal vascular access for a given patient should be determined by the nephrologist and access surgeon by taking into account (1) whether dialysis has been initiated, (2) the patient’s life expectancy, (3) whether the patient has had a previous failed vascular access, and (4) the likelihood of fistula nonmaturation. Careful clinical judgment should optimize vascular access outcomes and minimize prolonged catheter dependence among hemodialysis patients.

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Optimizing vascular access options remains a challenge in chronic hemodialysis patients (1). Over the past few years the Fistula First Initiative has strongly encouraged nephrologists, vascular access surgeons, and dialysis units in the United States to make valiant efforts to increase fistula use in the hemodialysis population (<http://www.fistulafirst.org>). This initiative has been hugely successful in achieving its primary goal: Between 2000 and 2008, fistula use increased from 24% to 52%, whereas graft use decreased from 58% to 22% (2,3). Unfortunately, there has been a concurrent increase in catheter use from 17% to 26%. At present, approximately 80% of U.S. patients initiate hemodialysis with a catheter (4). Moreover, there are long delays in achieving a mature fistula among such patients (5). Not surprisingly, prolonged catheter dependence has increased the frequency of catheter-related complications, including infection-related hospitalizations and mortality.

In contrast to the outcomes observed in Europe and Asia (6,7), the major hurdle to increasing fistula use in the United States has been the high frequency of primary fistula failure (fistula nonmaturation) due to early thrombosis or insufficient dilation to support repetitive cannulation with two dialysis needles. Older studies from approximately 30 years ago, in-

volving patients with relatively low comorbidity, only observed fistula nonmaturation in approximately 10% of patients (8–10). In contrast, more recent studies have reported a much higher likelihood of fistula nonmaturation, ranging between 20% and 60% (11–13). Simple clinical factors (older age, female sex, black race, vascular morbidity, and forearm location) have been repeatedly associated with fistula nonmaturation (11,14,15).

Preoperative vascular mapping has been touted as a useful approach to improve vascular access outcomes (16). It should theoretically improve fistula outcomes by providing the surgeon with detailed information about vessel diameter, stenosis, and thrombosis. Whereas preoperative mapping has been associated with a dramatic increase in fistula placement in several observational studies, it does not appear to reduce fistula nonmaturation (11). When evaluated in prospective studies, a high rate of fistula nonmaturation persists despite the use of routine preoperative vascular mapping to guide the surgeon in selection of optimal vessels for fistula creation. This was highlighted in a large National Institutes of Health multicenter randomized study in which 60% of fistulas created were not suitable for dialysis despite >75% with preoperative mapping (12). Nonmaturation continues to be higher in older patients, women, and forearm fistulas (12,15,17). Although some studies have demonstrated no association between vessel size and fistula maturation (18), most centers require a minimum arterial diameter of 2 mm and a minimum venous diameter of 2.5 to 3 mm (19). Selecting even higher vascular diameters would de-

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crease fistula placement without reducing fistula nonmaturation (20). Selective use of preoperative mapping has been found to be highly successful and more cost-effective than an “all-comer” approach (21). It is unclear what aspects of vascular mapping are critical for successful fistula maturation—vessel size, distensibility, reactive hyperemia, or other factors (19). Intuitively, results should be superior if the surgeon was able to perform their own vascular mapping before creating the patient’s fistula rather than reviewing a static report conducted by a technician (22). Clearly, surgical experience, selection, and technique affect the success of the fistula’s creation and maturation (23–25).

Postoperative intervention can facilitate fistula maturation and is required in 24 to 89% of all fistulas (26–30). The intervention rate ranges from 1.45 to 3.3 procedures per arteriovenous fistula (AVF) required for maturation, or 1.33 to 1.75 procedures per access-year (26,27,29). Most (70% to 80%) interventions will be successful (27,31,32), but it will take an additional 3 months, on average, until the AVFs are sufficiently developed for cannulation (32). Once an AVF is matured, the revision rate ranges from 0.17 to 0.57 per access-year (17,33–36), and revision is required in approximately 50% of AVFs (27,37).

Postoperative treatment with antiplatelet agents prevents early fistula thrombosis and should theoretically reduce fistula nonmaturation (38). The Dialysis Access Consortium study randomized 877 patients with new fistulas to receive clopidogrel or placebo for 6 weeks (12). Whereas clopidogrel significantly reduced early fistula thrombosis (12.2% versus 19.5%), a similar proportion of fistulas in both treatment arms were not suitable for dialysis within 6 months of their creation (61.8% versus 59.5%). An ongoing Australian randomized clinical trial is evaluating the effects of fish oil and aspirin on fistula outcomes (39). In addition, there are ongoing efforts to elucidate the pathogenesis of fistula nonmaturation in animal models (40,41). The extraordinarily high fistula nonmaturation rate observed in the Dialysis Access Consortium trial led the National Institute of Diabetes and Digestive and Kidney Diseases to sponsor a multicenter observational study, the Hemodialysis Fistula Maturation Consortium. This ongoing trial is evaluating the effect of demographic, clinical, biochemical, genetic, radiologic, surgical, and histologic factors on fistula maturation. The insights arising from this study should lead to future randomized clinical trials evaluating specific interventions to decrease fistula nonmaturation. Until we have proven interventions to improve fistula maturation, we must make the determination about the appropriate vascular access for each patient using clinical and preoperative mapping information.

One major justification for increasing fistulas has been that fistulas last longer than grafts (16). This statement is only true when the analysis is restricted to those vascular accesses that are successfully cannulated for dialysis. Primary graft failure is much lower for grafts than for fistulas, occurring in approximately 10% of grafts, even in recent studies (11,42). As a result of the striking differences in primary failure rates between fistulas and grafts, when primary failures are included in access survival analysis (*i.e.*, intent-to-treat analysis), cumulative fistula survival is no better than that obtained with grafts

(11,43,44). In fact, during the first 18 months after access creation, graft survival is actually superior to that obtained with fistulas (Figure 1). This last observation is particularly relevant in patients whose expected survival is unlikely to exceed 1 to 2 years. In this patient subpopulation, placing a graft first may dramatically lengthen the proportion of the patient’s lifespan with freedom from catheter dependence and its potential complications.

A recent study illustrated in stark details how advanced age might affect clinical judgment regarding choice of vascular access (45). This observational study compared fistula and patient survival in dialysis-dependent patients older or younger than 70 years of age. Cumulative fistula survival at 12 months was 68% in the younger patients, but only 39% in those over age 70. Patient survival at 18 months was 75% in the younger patients, but only 50% in those over age 70. Finally, among 23 elderly patients who died, only 35% had ever had their fistula used for dialysis. On the basis of these observations, one could argue for placing a graft rather than a fistula in catheter-dependent hemodialysis patients over the age of 70 years.

A second major justification for fistulas is that they require fewer interventions to maintain long-term patency for hemodialysis. The major limitation to graft longevity is their propensity for recurrent stenosis and thrombosis, which requires frequent angioplasties, thrombectomies, and surgical revisions to maintain their long-term patency for dialysis. The frequency of

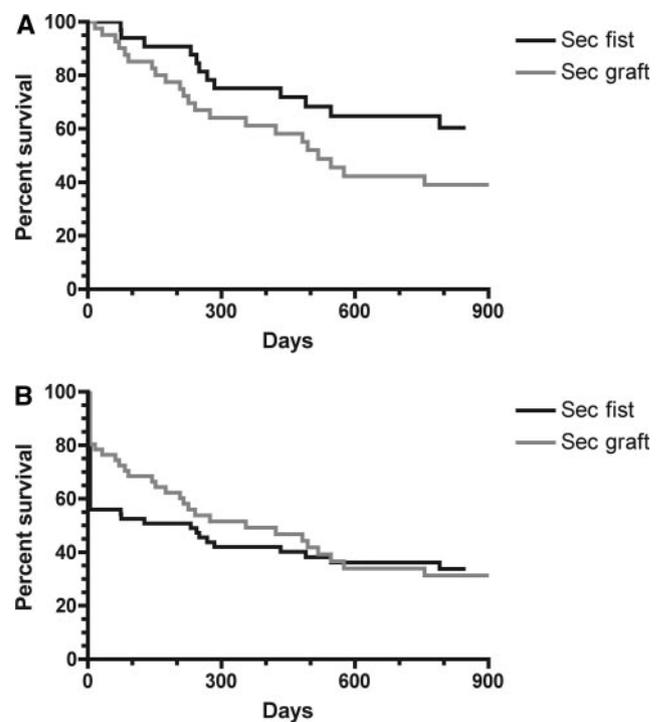


Figure 1. Cumulative access survival (A) excluding primary access failures ( $P = 0.03$ ) and (B) including primary access failures ( $P = 0.97$ ). Reproduced with permission from reference 46. Note that fistula survival was better than that of grafts only when primary failures were excluded. When primary failures were included, graft survival was better than that of fistulas for the first 18 months.

interventions is 3- to 6-fold higher for grafts than for fistulas (11). In addition, infections are more common in grafts than fistulas, but they are still much lower than for catheters (20). On the other hand, fistulas require more interventions than grafts to achieve maturation for dialysis (46). Nonmaturing fistulas frequently have an underlying anatomic problem, such as perianastomotic stenosis or presence of accessory veins, which can be visualized by an ultrasound or angiogram. Aggressive endovascular or surgical interventions to correct the underlying anatomic problem can frequently salvage an immature fistula and make it suitable for dialysis use (47–50). However, such interventions may have a negative effect on long-term fistula outcomes. Thus, a preliminary report found that immature fistulas requiring interventions to achieve maturation for dialysis had a shorter cumulative fistula survival as compared with those fistulas that did not require such interventions (51). In summary, although fistulas require more interventions to achieve maturation, grafts require more interventions to maintain long-term patency for hemodialysis (46).

Whereas a mature fistula may be superior to a graft, an immature fistula with prolonged catheter dependence is inferior to a working graft. Four major factors should be considered in the selection of optimal vascular access type in a given patient: (1) likelihood of early access complications, particularly nonmaturation; (2) likelihood of later access complications, primarily stenosis and thrombosis; (3) likelihood of catheter-related bacteremia and noninfectious catheter complications (particularly central vein stenosis); and (4) expected patient survival. At one extreme of the spectrum is a 25-year-old man with low vascular comorbidity who is not yet on dialysis. This patient has a relatively low likelihood of fistula nonmaturation. He has not yet initiated dialysis, so there is no risk of catheter-related bacteremia or central vein stenosis. Finally, he is likely to live many years on dialysis. Clearly, this patient is an ideal candidate for a fistula. At the opposite extreme is a 75-year-old woman with a history of myocardial infarction, stroke, and peripheral vascular disease who has already initiated dialysis with a catheter. This patient has a high likelihood of fistula nonmaturation (14). If a fistula is placed, she is likely to have prolonged catheter dependence with a high likelihood of catheter-related bacteremia (5). Finally, her life expectancy is only 1 to 2 years. This patient may be an ideal candidate for a graft. Of course, most patients fall somewhere in between these two extremes.

The Kidney Disease Outcomes Quality Initiative (KDOQI) vascular access guidelines list the order of preference for vascular access in the upper extremity as follows: forearm (radiocephalic) fistula, then brachiocephalic fistula, then transposed brachiocephalic fistula, and then a graft (16). This list of preferences is based on opinion and merits formal evaluation by randomized clinical trials. In addition, this recommended sequence potentially wastes valuable access sites, which is particularly important in dialysis patients with relatively long life expectancy. Thus, after a failed forearm fistula, placing a forearm graft (with a median survival of 2 years) as the next access would buy precious time before moving up to an upper arm vascular access. To address the specific KDOQI recommenda-

tions on vascular access sequence would require at least three separate trials: (1) comparing forearm fistulas to grafts, (2) comparing brachiocephalic fistulas to grafts, and (3) comparing transposed brachiocephalic fistulas to grafts. To date, only two randomized clinical trials comparing fistulas to grafts have been published, one addressing the first comparison, and the other addressing the third comparison (29,52).

The first study enrolled 182 patients whose preoperative vascular mapping revealed marginal forearm vessels at the wrist, defined as a radial artery diameter between 1 and 2 mm and/or a cephalic vein diameter  $\leq 1.6$  mm (29). These patients were randomized to receive a forearm fistula or graft. Fistula outcomes were inferior to those of grafts. Specifically, the respective 1-year primary patency of fistulas and grafts was 33% versus 44% ( $P = 0.035$ ) and their cumulative survival was 52% versus 79% ( $P < 0.001$ ). Moreover, surgical thrombectomy was required more frequently with fistulas than with grafts. The authors concluded that forearm grafts were superior to forearm fistulas in patients with truly marginal vessels. Many surgeons would likely not even attempt a forearm fistula or graft in such patients, but instead proceed directly to a brachiocephalic fistula, as recommended by the KDOQI guidelines. However, placing a forearm graft first may promote dilation of the upper arm veins such that a brachiocephalic fistula can be more easily placed once the forearm graft fails (53). Such an approach would also preserve precious vascular “real estate” in hemodialysis patients.

The second randomized study enrolled 105 patients with a failed radiocephalic and/or brachiocephalic fistula or those with vessels unsuitable for either fistula type (52). These patients were randomized to receive a transposed brachiocephalic fistula or a forearm loop graft. This study reported superior outcomes for the brachiocephalic fistulas than for the forearm graft. Specifically, the 1-year primary patency of fistulas and grafts was 46% versus 22% ( $P = 0.005$ ). This is not surprising because the intra-access blood flow in the upper arm is twice that of the forearm (54). Notwithstanding the differences in vessel size and blood flow, the cumulative access survival was similar for both groups (89% versus 85%), although the fistulas required fewer interventions to maintain patency for dialysis (1.7 versus 2.7 per patient-year,  $P = 0.02$ ).

Neither of these studies addressed the most common clinical scenario: patients with a failed forearm fistula or those with vessels unsuitable for creation of a forearm fistula. In this setting, KDOQI guidelines recommend creation of a brachiocephalic fistula in preference to a graft (16). Although there has been no randomized clinical trial comparing these two options, a retrospective study evaluated the relative merits of these two options in 110 patients with a previous nonmaturing forearm fistula (46). As compared with patients receiving a graft, those receiving an upper arm fistula had a higher primary failure rate (44% versus 20%,  $P = 0.006$ ), required more interventions to achieve maturation (0.42 versus 0.16 per patient,  $P = 0.04$ ), had longer catheter dependence (131 versus 34 days,  $P < 0.001$ ), and experienced more episodes of catheter-related bacteremia before permanent access use (1.3 versus 0.4 per patient,  $P = 0.003$ ). Median cumulative survival was superior for fistulas than for

grafts when primary failures were excluded (1524 *versus* 517 days,  $P = 0.03$ ) but similar when primary failures were included (231 *versus* 355 days,  $P = 0.97$ ) (Figure 1). Finally, once the vascular access was successfully cannulated for dialysis, fistulas required fewer interventions than grafts to maintain long-term patency for dialysis (0.73 *versus* 2.38 per patient-year,  $P < 0.001$ ). This analysis suggests that there are tradeoffs between fistulas and grafts. These tradeoffs might favor a fistula in some patients but favor a graft in other patients. Despite its retrospective design, this study offers sufficient equipoise to justify a multicenter randomized clinical trial comparing fistulas to grafts in a subpopulation of dialysis patients in which the superiority of fistulas over grafts is uncertain.

In such subpopulations in which the choice of a fistula *versus* a graft is not clear cut, how can we uphold the basic premises of Fistula First in providing the best access for the patient that will incur the fewest complications yet incorporate the specialized and often opposing viewpoints of the surgeons and nephrologists involved in the patient’s care? This can only be achieved by keeping the patient’s needs as the primary focus and by considering their individual clinical characteristics. Figure 2 provides a guideline algorithm that incorporates such principles. The three primary questions that must be answered are (1) the stage of chronic kidney disease, which indirectly incorporates issues of predialysis care, time and resources for access creation, maturation, and interventions for nonmaturing fistulas, and the potential risks and benefits of catheter use until the access can be reliably used; (2) the expected survival of the patient, to avoid procedures and costs associated with trying to achieve an unnecessarily long-term access that would outlive the patient yet simultaneously maintain quality of life and limit the risks associated with catheter use; and (3) prior access history, which demands understanding the reasons for prior failure and therefore considers the number and time required for potential necessary interventions for the future access. Lastly, the algorithm requires the clinicians to use their clinical and scientific acumen to determine the likelihood of the patient’s fistula to succeed or fail in providing reliable, prescribed dialysis and should facilitate communication between disci-

plines. For example, the considerations in determining the likelihood of a fistula maturing may differ between a nephrologist and a surgeon, whereby a nephrologist may weigh clinical, rather than vessel characteristics more heavily than a surgeon, whereas both are undoubtedly important.

Overall, in using the algorithm, the more one indicates “no” to the “bad” things, such as starting dialysis, short life expectancy, and previous failed access, the higher the likelihood that the most appropriate access is a fistula. In many instances, the most appropriate access for patients that fall within the two middle rows is unknown and should take into account individual circumstances. Clearly, it is time for randomized clinical trials comparing brachiocephalic fistulas and forearm grafts. We propose that one such multicenter study enroll patients who are already on dialysis (*i.e.*, catheter dependent), who have already had a radiocephalic fistula that failed to mature or have no suitable vessels for a forearm fistula, and whose expected patient survival is  $<2$  years. These patients fall into the middle two rows of the algorithm on choosing a fistula or graft, where the most appropriate vascular access for the patient is unknown. These patients would be randomized to receive an upper arm fistula or a forearm graft. One example of an important primary outcome would be total time on dialysis without catheter dependence. Secondary outcomes could include time to freedom from catheter dependence; number of catheter-related bacteremias; number of interventions to maintain access patency; number of access-related hospitalizations; and the financial costs associated with the creation, maintenance, and complications of having a fistula *versus* a graft.

Medicine should not be practiced by administrative fiat but should be based on the best available evidence. Whenever there is reasonable disagreement and clinical equipoise about the optimal medical management of a patient, a randomized clinical trial is indicated to answer the question. Thus, for example, many nephrologists were convinced on the basis of observational data that a  $Kt/V > 1.2$  would improve hemodialysis patient outcomes, until the Hemodialysis Study refuted this belief (55). Similarly, the long-held belief that hemoglobin should be normalized in chronic kidney disease patients was refuted by several randomized clinical trials that showed this

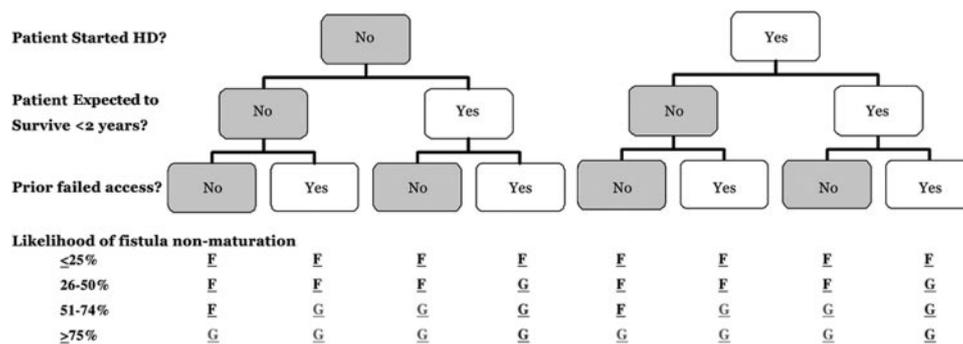


Figure 2. An algorithmic guide to choosing an appropriate hemodialysis vascular access for patients. This protocol requires the nephrologist and access surgeon to consider three important clinical factors: timing of access surgery relative to initiation of hemodialysis, life expectancy of the patient, and prior failed vascular access. This information, along with the likelihood of AVF nonmaturation, is used to determine the most appropriate vascular access for that patient. F, fistula; G, graft.

practice to be ineffective or even harmful (56–58). With respect to the choice of vascular access, the current inertia created by the KDOQI guidelines, Fistula First Initiative, dialysis network expectations, and dialysis provider “report cards” stipulates that fistulas are the preferred access. It is time for us to acknowledge that the rigid “fistula first” recommendations are not based on solid, current evidence-based data and may be harmful to some hemodialysis patients by subjecting them to prolonged catheter dependence with its attendant risks of bacteremia and central vein stenosis.

Only a definitive study can provide an objective answer to this debate. To provide clinically meaningful answers will clearly require large, multicenter studies. The number of patients required for such a study will depend on the choice of primary outcome selected and the estimated event rates. Canadian-based funding organizations (Canadian Institute of Health Research and Physician Services Incorporated) have recently funded a pilot study to assess the feasibility of and arrive at power calculations for a large, multicenter study comparing fistulas to grafts. It is likely that the sample size required for such a study would be similar to that enrolled in the Dialysis Access Consortium fistula and graft trials (approximately 650 to 900 patients) (12,42). Although such studies will be expensive, it is not unreasonable to expect support from various funding agencies, including government-based agencies, given the enormous cost of vascular access and ESRD care and its effect on healthcare costs. In this regard, the U.S. government has recently provided \$1.1 billion in funding for research on comparative effectiveness of drugs, medical devices, and surgical procedures (59). The time is right for the nephrology community to support randomized clinical trials comparing fistulas to grafts in high-risk hemodialysis patients.

## Disclosures

None.

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