33. Hultin LE, Hausner MA, Hultin PM et al. CD20 (pan-B cell) antigen is expressed at a low level on a subpopulation of human T lymphocytes. Cytometry 1993; 14: 196–204

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Fistula-first and catheter-last: fading certainties and growing doubts

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In this issue of Nephrology Dialysis and Transplantation, Grubbs et al. [1] present USRDS data on the association between vascular access type at hemodialysis initiation and 6-month mortality in 117,277 patients who started hemodialysis therapy between January 2005 and December 2007. Thanks to additional access information included in the End-Stage Renal Disease Medical Evidence Report (form CMS-2728) since 2005 [2], the authors were able to classify the initial hemodialysis access as either fistula alone, graft alone, catheter with maturing fistula, catheter with maturing graft or catheter alone. The authors found that, compared with people using a fistula, the risk of death from all causes was progressively higher in people using grafts, in those using catheters with a maturing fistula, in those using catheters with a maturing graft and in those using catheter without a maturing arteriovenous access. Six-month mortality data were similar to long-term results from a previous analysis of USRDS data [3]. Grubbs et al. [1] also reported that the relative risk of death associated with the use of catheters alone versus fistulas alone was 1.95 in unadjusted analysis, 1.69 after standard adjustment and 1.54 in a fully adjusted analysis that included information on patient health status. Although the attenuation of the strength of the association between access type and mortality was larger from unadjusted analysis to an analysis controlled for standard confounders (21% on a log-scale), inclusion of health status in the adjusted model further decreased the relative risk (by 18%). Of note, the authors found that the probability of limited functional status (i.e. institutionalization, inability to ambulate or transfer, or assistance required for the activities of daily living) was progressively higher in those using grafts (18.8%) and catheters with (23.5%) or without a maturing arteriovenous access (25.5%) compared with people...
using a fistula (10.8%). In addition, and consistent with functional status data, people using a fistula spent fewer days in hospital in the 2 years preceding hemodialysis initiation (5.4 days on average) when compared with those with a graft (10 days), a catheter and a fistula (12.1 days), a catheter and a graft (16 days) or a catheter without an arteriovenous access (18 days).

Interestingly, the authors propose an interpretation of their data that challenges the widely-accepted fistula-first/catheter-last approach to the optimal access type for hemodialysis. They suggest that risk attenuation in progressively adjusted models may indicate the existence of selection bias, whereby healthier patients are more likely to use a fistula for hemodialysis (and sicker patients a catheter), and that residual (unmeasured) confounding may persist after adjustment, making uncertain the true risk attributable to access type. This view is consistent with our recent systematic review of the association between access type and clinical outcomes, in which we found a high risk of bias, especially selection bias, in all available studies [4].

Publication of this study and the discussion that may follow are timely given that at present all vascular access guidelines worldwide and are being actively promoted on a local, national and international level. Canadian, American and European guideline statements [5–7] cite evidence from observational studies that fistulas are associated with the best patient survival, the lowest risk of complications and are the least expensive form of access to create and maintain. Further, the proportion of individuals treated with fistulas is considered a proxy for the quality of care in hemodialysis programs and some organizations, such as the National Health Service (NHS), even tie funding to the attainment of fistula utilization targets [9].

This has prompted initiatives to increase the use of fistulas like the Ontario Dialysis Access Initiative [10], the Canadian Society of Nephrology Vascular Access Working Group [11], and the Fistula First Breakthrough Initiative in the USA [12].

Although pressure to hit fistula utilization targets is intensifying and the support for these initiatives is increasing, the quality of the evidence on which they are based is low [4]. There has never been a randomized comparison of different access strategies with mortality or other hard endpoints as the outcome, and the observational literature that established the superiority of fistulas has important limitations. All large observational studies published so far have compared access achieved as opposed to the access that was intended or planned [4]. Since attempts at fistula creation are unsuccessful in 23% [13] to 60% [14] of the cases, and several procedures are often necessary to achieve a functioning fistula particularly in subjects with poor prognosis [15], the catheter group in most studies includes people in whom a fistula has been attempted but failed, or in whom it has not been attempted because of poor prognosis. These studies may have overstated the benefits of fistulas. Adoption of health-care practices with insufficient evidence for safety or efficacy (in this case promoting a fistula strategy as the best access strategy) may lead to unintended consequences for patients (e.g. the need for repeated invasive procedures and potential complications) or the health-care system (e.g. increased costs and inefficient use of resources). Prior examples include the widespread adoption of hormone replacement therapy in postmenopausal women to prevent cardiovascular disease [16] or erythropoiesis-stimulating agents in patients with chronic kidney disease to normalize hemoglobin levels until randomized trials demonstrated that such interventions were harmful [17].

When assessed against recommended standards [18], the risk of bias in studies comparing clinical outcomes by hemodialysis access type is substantial [4]. Figure 1 summarizes the potential sources of bias in the existing literature, which we briefly discuss hereafter.

1. Selection bias 1—Inclusion of patients who start dialysis urgently: Catheters are the only access that can be placed and used immediately for hemodialysis and as a result, nearly all patients who start dialysis urgently are treated with a catheter [19]. Individuals who start dialysis urgently, however, have twice the risk of adverse events, including death (odds ratio 2.09; P-value <0.001) [19]. This makes it difficult to determine if the poorer outcomes observed in patients treated with catheters are caused by the catheters, or are simply due to the fact that the sickest patients are treated with them (i.e. confounding by indication). A recent small, retrospective study provided insight into the potential magnitude of this bias. The relative hazard of death in patients treated with catheters as their first form of dialysis access was compared with patients using a ‘permanent’ form of access (fistula for hemodialysis or peritoneal dialysis catheter for peritoneal dialysis). In an analysis of all patients starting dialysis, the hazard for death was 70% higher in patients treated with catheters compared with those with a permanent access, but when those starting dialysis urgently were removed from the analysis, there was no significant difference in outcomes (adjusted HR: 1.03; 95% CI: 0.67–1.57) [20].

2. Selection bias 2—Inclusion of patients who are ineligible for a fistula: In clinical practice, the only patients faced with a choice between fistulas and catheters are those who are eligible for both, and this is the group that should be studied. Individuals who are not eligible for fistulas appear to have a higher risk of mortality (3-year survival 81 versus 26%; P < 0.0001) and have traditionally been included in the catheter cohort in these types of analyses [21]. Eligibility criteria for fistula attempts are not well defined and some argue that most patients are potential candidates for a fistula. In practice, individuals with a life expectancy of <1 year and those who have severe, decompensated heart failure and would not tolerate a fistula are
usually not considered eligible for a fistula attempt [22]. It is difficult to address the consequences of this selection bias outside of a randomized comparison.

(3) Selection bias—Failure to analyze data according to the intention-to-treat principle: Prior studies have compared outcomes based on the achieved form of vascular access (access ultimately used), rather than the intended or attempted access (planned strategy) [4]. Prior observational studies have compared people who had successful fistula attempts to all people using a catheter, including those treated with a catheter because they were not eligible for a fistula (e.g. due to comorbidity or life expectancy <1 year), or because their fistula attempt was unsuccessful. This is relevant because 23–60% of fistula attempts fail and failure is more likely to occur in the elderly, obese and those who have more severe peripheral vascular disease, coronary artery disease and diabetes mellitus [14, 15]. In an intention-to-treat analysis these people would be included in the fistula group, with potential attenuation of the expected benefits of a ‘fistula-first’ strategy.

(4) Information bias—Failure to report all access-related outcomes: Since the use of a catheter may simply be a surrogate for a poorer prognosis, it is important to distinguish between outcomes that occur because a patient has a poor prognosis and those that are a direct consequence of their access. Most observational studies comparing catheters and fistulas have not made this distinction, and information about whether mortality was access-related was not available [4]. For example, most key opinion leaders in this area agree that the excess mortality related to catheter use is attributable to infectious complications, and specifically, to catheter-related bacteremia [23]. However, the rates of catheter-related bacteremia in Canadian programs are lower than 0.5 events per 1000 catheter days, or one catheter-related bacteremia every 5.5 years [24], and we recently found that they were responsible for only 7% of hospital admissions in hemodialysis patients [21]. Given that only a small percentage of these events are fatal, it is difficult to explain a 53% higher risk of mortality (~10% absolute annual risk) in patients treated with catheters [4].

(5) Ascertainment bias—Differential surveillance for outcomes: The vascular access is often considered responsible for infections in the hemodialysis population. However, bacteremia episodes are more often labeled ‘catheter-related’ rather than ‘access-related’, and very rarely ‘fistula-related’. As a result, in clinical practice, and in observational studies, there is more intense surveillance for bacteremia among catheter users, with the risk of differential ascertainment and bias. Other potential consequences of fistula creations, such as left ventricular hypertrophy [25] and pulmonary hypertension [26], may be understudied.

Obviously, the high risk of bias identified in available evidence has important clinical and research implications. For example, the increased risk of death attributable to catheters, if it exists, may be smaller than expected. Only a clinical trial can address this research question. But what do patients and physicians think? Which research questions and which outcomes are of interest to patients and physicians? We developed the Vascular Access Questionnaire (VAQ) to measure patient views of their vascular access [27]. The VAQ was shown to be
reliable (Cronbach’s alpha 0.77) and was administered to 222 hemodialysis patients (118 dialyzing with a fistula and 104 dialyzing with a catheter) at 2 regional dialysis programs in Toronto, Canada. Higher VAQ scores indicate a higher burden of symptoms related to their vascular access. Overall, there was no difference in the mean VAQ symptom score (mean 6.2 in fistula group versus 5.4 in catheter group; P-value 0.36), but there was a significant interaction between access type and age (P-value for interaction term <0.01). Elderly patients had lower symptom scores with catheters compared with fistulas (VAQ score 4.0 versus 7.0) and were more likely to be bothered by bleeding and bruising complications than younger patients. Given that more than half of the hemodialysis patient population is over 65 and that the fastest growing segment is over 75 years of age, this is a very relevant finding. It emphasizes the need to prove the superior efficacy of a fistula strategy compared with a catheter strategy in a randomized trial if we are going to actively promote a form of access that is associated with worse symptoms in elderly patients. In another survey Canadian nephrologists indicated willingness to participate in a randomized comparison of catheters to fistulas in the elderly, including comparison of patient-centered end points (Dr R.R. Quinn; ongoing study). This survey is currently being conducted in Australia (Dr K.R. Polkinghorne; personal communication) and Europe (Dr W. Van Biesen; personal communication). We believe that a randomized trial of benefits and harms of different access strategies will have to include cost and quality of life data among the outcomes.

In conclusion, the study by Grubbs et al. [1] present data that are consistent with current literature indicating increased risk of mortality associated with use of catheters. However, relative risk attenuation after adjustment for indicators of patient health status and the high risk of bias in existing studies suggest that residual confounding may persists, making uncertain the true strength of the association between access type and patient outcomes.

CONFLICT OF INTEREST STATEMENT
The authors declare that they have no conflict of interest.

(See related article by Grubbs et al. Health status as a potential mediator of the association between hemodialysis vascular access and mortality. Nephrol Dial Transplant 2014; 29: 892–898.)

REFERENCES

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