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See related article, “Multiple Genes of the Renin-Angiotensin System Are Novel Targets of Wnt/ β -Catenin Signaling,” on pages 107–120.

Catheter Last, Fistula Not-So-First

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J Am Soc Nephrol 26: 5–7, 2015.
doi: 10.1681/ASN.2014060594

The issue of vascular access choice is not as black and white as the Centers for Medicare & Medicaid Services (CMS) would like it to appear, with arteriovenous fistula (AVF) always being good or “first” and central venous catheters (CVCs) always being bad or “last.” Nonetheless, CMS has instituted a quality incentive program (QIP) for dialysis providers that rewards high AVF prevalence and penalizes high CVC prevalence without regard to patient mix. For payment year 2014, vascular access constitutes 30% of the total QIP score.¹ This may have already led to access to care issues, as some dialysis providers are refusing to accept patients with CVCs. CMS has recently given ground on this issue by renaming the “Fistula First” initiative “Fistula First Catheter Last” (FFLC) to emphasize that CVC avoidance is as important or more important than AVF use.²

It is noteworthy that the increase in prevalent AVF rates—from around 30% to around 60%—since the Fistula First project began has been accompanied by a reciprocal decline in arteriovenous graft (AVG) prevalence and only a small decline in CVC prevalence.³ This reflects what might be a misguided priority for getting AVFs into all hemodialysis patients over

getting CVCs out. Recently there has been some discussion in the literature that this “one size fits all” approach is inappropriate for patients in whom the time and effort required for the placement and maturation of a functional AVF are not balanced by the expectation that the AVF will function longer and with fewer complications than an AVG.

Lok *et al.* proposed a formula that uses patient age, presence of coronary artery disease, presence of peripheral vascular disease, and race to determine risk for AVF maturation failure. Patients with the lowest score had a 35% AVF failure-to-mature rate, and patients with the highest score had a 71% rate.⁴ When this formula was applied to almost 200,000 incident hemodialysis patients from 2005 to 2009, based on data obtained from the Medical Evidence Report (CMS Form 2728), AVF use at dialysis initiation varied from 25.6% in patients at “low risk” for AVF maturation failure to 19.0% in the “very high risk” patients. This finding demonstrates the limited ability of the clinical risk factors identified by Lok *et al.* to predict incident AVF use. This retrospective study identified female sex, black race, Hispanic ethnicity, age older than 85 years, diabetes, peripheral vascular disease, congestive heart failure, other cardiac disease, and low body mass index as risk factors for failure to have a functioning AVF at the time of hemodialysis initiation. Hypertension, obesity, private insurance, and more time under a nephrologist’s care were associated with a greater likelihood of a having a functional AVF at the time of hemodialysis initiation.⁵

Because AVFs have a primary failure rate of 30%–70% and a 1-year patency rate of 40%–70%, many patients will undergo multiple procedures over many months in the attempt to establish AVF access, which may or may not succeed.^{6–9} The patients in whom the benefit of AVF over AVG placement is most suspect are those with limited life expectancy (advanced age being a surrogate) and those with poor blood vessels (advanced age, female sex, and presence of diabetes being surrogates).

The article by Drew *et al.* in this issue of *JASN*¹⁰ tests the hypothesis regarding the predictive value of these factors in determining the superiority of various vascular access types (AVF, AVG, and CVC) by using a decision analysis method. Of note, this method was originally championed by two nephrologists, Schwartz and Kassirer, in the 1970s¹¹ but has not been commonly used in the nephrology literature other than by the decision analysis disciples at Tufts University. It is a useful method to quantify outcomes and costs of various diagnostic and therapeutic choices under many variables. Thanks to the Dialysis Outcomes and Practice Patterns Study and the US Renal Data System, most of the required outcome and cost data to perform the modeling are available.

As might be predicted, the incremental survival of patients with AVFs is most robust in patients with the best vessels (young, male, nondiabetic) and declines with patient age, presence of diabetes, and, to a lesser extent, female gender. Not surprisingly, elderly patients have very little survival benefit with AVFs over AVGs and CVCs because their lifespan is too short for the long-term benefits of AVFs to accrue. Sixty- and 80-year-old diabetic women actually have better survival with

Published online ahead of print. Publication date available at www.jasn.org.

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AVGs over AVFs, and only three categories of patients (40-year-old diabetic women, 60-year-old nondiabetic women, and 80-year-old nondiabetic women) have both lower costs and superior survival with AVFs versus AVGs. Sensitivity analyses using different cost and access patency assumptions by and large made the incremental cost-effectiveness of AVFs over AVGs less favorable. One can argue about the validity of the assumptions in the base-case and sensitivity analyses, but the inevitable conclusion is that the incremental cost-effectiveness of AVFs over AVGs is subject to many patient-specific factors, many of which are intuitive and easily identifiable from the ESRD Medical Evidence Report (sex, age, presence of diabetes). This is in contrast to the complex and less easily retrievable case-mix adjusters that go into the standardized mortality ratio and standardized hospitalization ratio, for example.

Several recent publications have challenged the desirability of AVFs over AVGs in elderly patients in particular,^{12,13} yet there is no case-mix adjustment for age in the QIP measure for AVF prevalence. CMS policy for the ESRD program is driven by its “Triple Aims”: (1) better care for the individual through beneficiary- and family-centered care, (2) better health for the ESRD population, and (3) reduced costs of ESRD care through improved care.¹⁴ This approach does not acknowledge that “better” care for an individual, and even less expensive care for an individual, may conflict with policies, such as the vascular-access QIP, that are based on population studies. The population studies on which the FFLC and vascular-access QIP are based are all observational and therefore subject to confounding. The Kidney Disease Outcomes Quality Initiative and Kidney Disease Improving Global Outcomes clinical practice guidelines based on this suboptimal evidence are designed as clinical decision making tools, not as standards of care. CMS cites the “performance gap” between the states with the highest prevalent AVF rates (around 73%) and the states with the lowest prevalent AVF rates (around 53%)³ as evidence that opportunities to improve AVF prevalence remain. However, this population approach ignores the unique characteristics and preferences of individual patients and their caregivers.

Although AVGs require more interventions to maintain patency than AVFs, their cumulative patency is the same when primary AVF failures are factored in.¹⁵ The longer maturation time and high primary failure rate of AVFs lead to longer periods of catheter dependence and more catheter-related complications. Costs for AVFs may exceed those for AVGs, as they did in certain patient subgroups in Drew and colleagues’ report,¹⁰ because of the numerous procedures that may be required for the former to establish patency and the complications from prolonged catheter use. As observed by Allon and Lok, there is equipoise about the relative merits of AVFs versus AVGs in patients with moderate to high risk of AVF nonmaturation.¹⁵ Only randomized controlled trials of AVFs versus AVGs in various subsets of hemodialysis patients will provide the needed evidence to eliminate confounding and establish the most cost-effective vascular access. The characteristics of these subsets can then be used as evidence-based

case-mix adjusters for the QIP vascular-access measures. A low catheter prevalence rate (“catheter last”) should trump a high AVF prevalence rate in the QIP scoring to acknowledge those subsets of patients in whom an AVG is more suitable than an AVF. In any event, a patient-centered approach with appropriate education of the patient and family, evaluation for the availability of suitable vessels for AVF creation, and consideration of the patient’s life expectancy and time to dialysis initiation should drive vascular access choice over the incentive to receive a higher score on the QIP vascular-access measures.

Vascular access is only one example of the paradox between patient-centered care and quality metrics based on population studies. The role of a patient-centered approach to the management of anemia in patients with CKD is another example.¹⁶ Reconciling this paradox is what clinical judgment is all about and why physicians cannot be replaced by algorithms, care paths, and “cookbook medicine.” AVFs are the preferred vascular access in the hemodialysis population but not in every individual or even in certain subsets of that population; this is a very important distinction. Until randomized controlled trials are published to provide more focused, patient-centered evidence on vascular access choice and CMS makes allowances in the QIP vascular-access measures for such evidence, the nephrologist must continue to defend an individualized approach to vascular access based on the patient’s situation and the evidence available. In most cases (currently >60% in the United States³), that will favor an AVF, but increasing evidence supports the determination for the other 40% that it will not.

DISCLOSURES

None

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See related article, "Vascular Access Choice in Incident Hemodialysis Patients: A Decision Analysis," on pages 183–191.

The Biomarker Niche for Fibroblast Growth Factor 23 Testing in CKD

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J Am Soc Nephrol 26: 7–9, 2015.
doi: 10.1681/ASN.2014060621

Identifying strategies to prevent progression of CKD, reduce risk of its cardiovascular complications, and improve survival is

Published online ahead of print. Publication date available at www.jasn.org.

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among the highest priorities in nephrology. Progress on these initiatives has been impeded by lack of validated biomarkers of early kidney injury that offer prognostic value beyond quantification of eGFR and albuminuria. Given its strong independent associations with CKD progression, cardiovascular disease, and death, fibroblast growth factor-23 (FGF-23) has emerged as a novel biomarker candidate in CKD.^{1–3}

FGF-23 was originally discovered in studies of autosomal dominant hypophosphatemic rickets and tumor-induced osteomalacia, which are rare disorders caused by high circulating concentrations of FGF-23.^{4,5} Since these seminal findings, an explosion of laboratory-based, patient-oriented, and epidemiologic research has helped characterize many aspects of FGF-23 regulation, its classic functions and off-target effects, and the potential clinical implications of high circulating levels.⁶ Among the many important themes to emerge from this body of translational research is that CKD is one of the ripest clinical settings for developing FGF-23 as a clinical test of the future. A large epidemiologic study reported in this issue of *JASN* adds an important new chapter to the FGF-23 chronicle in CKD.⁷

Numerous studies have demonstrated that FGF-23 levels rise early in the course of CKD,^{8,9} but few have tested the converse: Can the early increase in FGF-23 be leveraged as a diagnostic or confirmatory test for the presence of early CKD itself? Representing the Chronic Kidney Disease Biomarkers Consortium, Rebholz *et al.* tested the hypothesis that higher FGF-23 levels are associated with increased risk of developing kidney disease.⁷ They conducted their analyses within the Atherosclerosis in Communities (ARIC) study, a large, community-based, prospective cohort study. In their primary analyses, the investigators examined a single measurement of baseline intact FGF-23 as a risk factor for incident ESRD in 13,448 participants who had a mean baseline eGFR of 97 ml/min per 1.73 m²; 2% were <60 ml/min per 1.73 m². During a median follow-up period of 19 years, 267 (2%) participants developed ESRD. In unadjusted analyses, the highest versus the lowest quintile of FGF-23 was associated with a nearly 5-fold higher risk of developing ESRD. As expected, baseline eGFR was the most important confounding variable, but the significant association between higher FGF-23 and risk of incident ESRD persisted after adjusting for eGFR, regardless of which estimating equation was used. Further adjustment for other risk factors, including calcium, phosphate, and parathyroid hormone levels, did not alter the results. In a sensitivity analysis, the results remained qualitatively unchanged after additional adjustment for albuminuria in the subgroup of approximately 80% of participants in whom these assessments were available. Emphasizing the eGFR-independent effect, higher FGF-23 levels (only on the continuous scale) remained independently associated with higher risk of ESRD when the analysis was restricted to individuals with baseline eGFR >90 ml/min per 1.73 m².

In their secondary analyses, the research team tested whether higher FGF-23 levels were also independently asso-