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See related article, "The Mitochondrial-Targeted Compound SS-31 Re-Energizes Ischemic Mitochondria by Interacting with Cardiolipin," on pages 1250–1261.

Vascular Access for Hemodialysis in Older Adults: A "Patient First" Approach

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In their landmark 1996 paper in *JAMA*, Hirth and colleagues reported that most patients in the United States with permanent vascular access were undergoing dialysis *via* a prosthetic graft rather than an autogenous fistula, despite known higher rates of infection and thrombosis associated with grafts.[1] These authors also reported large regional differences in rates of graft use—ranging from 23% of patients with a permanent access in New England to 85% in the East South Central census region—that were not explained by variation in patient characteristics.

These observations served as a wake-up call to the renal community, which responded with a series of initiatives to increase fistula use.[2] In 1997, the Kidney Disease Outcomes Quality Initiative (KDOQI) published clinical practice guidelines for hemodialysis vascular access that strongly favored the use of fistulas over grafts. In 1998, the Health Care Financing Administration (now Centers for Medicare and Medicaid Services [CMS]) developed clinical performance measures for vascular access that included target fistula and catheter

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rates. In 2003, CMS partnered with the ESRD networks to implement the Fistula First initiative, a continuous quality improvement initiative intended to translate KDOQI guidelines into clinical practice.

Collectively, these efforts have dramatically reshaped patterns of permanent access use in the United States. As a result, most patients with permanent access now undergo dialysis *via* an autogenous fistula.[3] More recently, Fistula First has turned its attention toward reducing catheter use because it has become clear that policies to promote fistula use have not had the intended effect of reducing catheter reliance.[3–6]

Despite the success of these initiatives in reducing rates of graft use among patients of all ages, some authors have questioned the appropriateness of a "fistula first" approach in older adults.[7,8] Because the theoretical advantages of fistulas over grafts do not accrue immediately, there is concern that patients with more limited life expectancy may not survive long enough to reap the benefits of having a fistula.[9,10] Although grafts require more procedures to maintain patency, fistulas require more procedures to establish patency, with the result that overall patency may not differ substantially between the two forms of permanent access.[11,12] This may be an especially important consideration in older adults because of their more limited life expectancy and increased risk of failed fistula maturation.[9,10,13] In this issue of *JASN*, DeSilva and colleagues provide new information relevant to this dialogue.[14] These authors describe survival among patients age 67 years and older who initiated long-term dialysis from 2005 to 2008 as a function of the type of vascular access first placed. In contrast to several prior studies reporting higher mortality rates in patients with a graft versus those with a fistula at the time of initiation, mortality rates for members of this cohort whose first access was a graft were similar to those for patients whose first access was a fistula. This was especially true in patients age 80 years and older, among whom mortality did not significantly differ by type of first permanent access placed. As described in other studies, mortality rates among patients with catheters at onset of dialysis were much higher than for patients who had received a graft or a fistula, and this was true for all age groups. Overall, 43% of patients who had received a fistula as their initial form of permanent access initiated dialysis with a catheter compared with 25% of those who had received a graft. These findings add to a growing body of work questioning the wisdom of a "fistula first" approach in older adults and arguing for greater flexibility in choice of hemodialysis access.[7–10,15,16]

A limitation of policies intended to optimize vascular access for hemodialysis in this country has been a failure to take into account the complexities and challenges of the illness experience of individual patients with CKD. Strategies focusing on preferred and least preferred forms of vascular access fail to recognize that the relative benefits and harms of each form of access are critically dependent on the characteristics, circumstances, prognosis, preferences, and goals of individual patients.[9,10,15,16] Because of heterogeneity in life expectancy, health status, health priorities, and illness experiences, no one approach to vascular access—whether "graft first," "fistula first," or "catheter last"—can be expected to meet the needs of all older adults with advanced kidney disease.[7,9] Further, the traditional outcomes examined in studies of vascular access, such as survival, infection, hospitalization, and costs, may not be those that matter the most to individual patients. A qualitative study conducted among 13 Canadian hemodialysis patients who had elected to receive chronic dialysis *via* a catheter identified adverse personal or vicarious experience with a fistula related to cannulation, bleeding, time commitment, and/or appearance as factors driving this decision.[17] Others expressed a desire to maintain the status quo even when they understood the risks associated with catheter use.

Because many older patients with severe reductions in estimated GFR never go on to initiate dialysis,[15] efforts to secure a functional fistula by the time of initiation may require that some accept the harms of a procedure from which they may never benefit.[16,17] And even in situations where fistula placement would clearly be beneficial, older adults with advanced kidney disease (who often have a variety of other health conditions) may need to prioritize other, more pressing health concerns over fistula placement.[18,19] Patients may themselves be uncertain about whether they would want dialysis should the need arise and may be unwilling to undergo fistula or even graft placement when there are so many unknowns.[20] One of my own patients, who agonized over this decision, identified uncertainty about "what kind of shape [he] would be in" when dialysis was needed as a major barrier to fistula placement. By failing to situate discussions about vascular access in the wider context of downstream treatment decisions about dialysis and desired treatment intensity toward the end of life,[21] we may overlook those concerns of greatest import to the patient and risk committing some patients to a cascade of unwanted and potentially harmful interventions.

The findings of this study—that among older adults approaching dialysis, initial choice of permanent access does not greatly affect survival after initiation, and that those who receive a graft are less likely than those who receive a fistula to require a catheter at initiation—provide useful insights that may help to guide clinical decision-making. However, these results should be interpreted with the following considerations in mind. First, this study evaluated only the association between type of access and mortality and did not include other outcomes that may shape clinical decisions about vascular access. Second, it is not at all clear whether the association between type of access and survival reported in some prior studies reflects a true treatment effect versus the effect of unmeasured confounding. Third, while the authors designed this study as an intention-to-treat analysis, the analyses presented here do not really replicate real-world clinical decision-making because they do not include patients who underwent permanent access placement but did not initiate dialysis.

In shifting our focus from the population to the individual patient to develop a more patient-centered approach to access

planning, metrics that capture information on type of access selected (*e.g.*, rates of fistula, graft, and catheter placement) become less relevant than those that characterize the process of access selection and the extent to which this meets the needs of individual patients. Ideally, this process should accomplish several goals: allowing clinicians to appreciate the unique experience, perspective, and goals of individual patients; helping patients and their families to better understand available treatment options and associated risks and benefits; and ensuring that patients and clinicians have an opportunity to share in decisions about vascular access.[22–24] Most helpful in supporting shared decisions about vascular access will be efforts to enhance communication and knowledge transfer between patients and clinicians[25] and to generate outcome data that provide patients and clinicians with realistic expectations about different treatment options.[26]

To optimally meet patients' needs, the process of choosing an access will often need to be dynamic in order to accommodate changing circumstances, health status and preferences, and interdependence between different types of access.[27,28] Input from patients and other stakeholders should also be integral to any efforts to advance the field. For example, interventions to promote timely fistula placement might benefit from a better understanding of barriers to and facilitators of timely placement from the perspectives of patients, families, and clinicians. Efforts to support a more flexible approach to access placement would benefit from a better understanding of what outcomes matter most to patients. Input from patients and other stakeholders should also be instrumental in prioritizing among the many possible research strategies and initiatives intended to improve outcomes related to vascular access.

To deliver care that is truly centered on the patient, we may ultimately need to set aside traditional metrics focusing on universal treatment targets (*e.g.*, rates of fistula, graft, and catheter use) in favor of new ones focusing on the extent to which the process and outcomes of access selection support the goals and preferences of individual patients.[29]

DISCLOSURES

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See related article, "Fistula First Is Not Always the Best Strategy for the Elderly," on pages 1297–1304.

Can Genetics Risk-Stratify Patients with Membranous Nephropathy?

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Membranous nephropathy (MN) is the leading cause of primary nephrotic syndrome in white adults and a major cause of nephrotic syndrome across global populations. In MN, circulating antibodies permeate the glomerular basement membrane and, in the subepithelial space, form immune complexes with antigens on podocyte membranes. Recently, the M-type phospholipase A_2 receptor (PLA_2R) was identified as the specific podocyte antigen responsible for eliciting immune complex formation with circulating antibodies. Anti-PLA_2R antibodies are detected in 60%–75% of idiopathic MN cases across many ethnicities.[1,2] Additional podocyte autoantigens—mitochondrial SOD 2, aldose reductase, α-enolase, and neutral endopeptidase[3,4]—have likewise emerged as potential targets of MN-specific autoantibodies, potentially filling in the missing gaps in PLA_2R antibody-negative disease. These breakthroughs have established MN as a disease of autoantibodies and, in many ways, challenge the continued use of the term *idiopathic MN*.[5] Nonetheless, we still do not know why, exactly, such autoantibodies develop in MN. The identified podocyte antigens are endogenously expressed; only the autoantibodies against such antigens are detected in patients with MN.

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Previous case reports of familial forms of MN have suggested a genetic predisposition to disease.[6] In a recent genomewide association study (GWAS) in three European populations (French, Dutch, and British), Stanescu *et al.* described associations of MN with the HLA locus on chromosome 6p21 and the *PLA2R1* locus (encoding PLA_2R) on chromosome 2q24.[7] The association with HLA was significant in all three patient samples, whereas the association with *PLA2R1* was significant in the Dutch and British samples (as well as in joint analysis of all three populations). Strikingly, whereas the risk of disease was relatively modest in individuals with risk alleles at any one locus, the odds ratio for MN was an astronomical 78.5 (95% confidence interval [95% CI], 34.6 to 178.2) in individuals homozygous for risk alleles at both loci, indicative of strong genetic interaction. This GWAS was thus unusual because the effect sizes imparted by the combined risk alleles were very large, suggesting a potential role for genetics for noninvasive screening or risk stratification of MN. This study also provided an independent line of evidence implicating *PLA2R1* in the pathogenesis of disease, suggesting that sequence variants within *PLA2R1* may alter expression or function of PLA_2R, potentially unmasking it as an autoantigen that, in conjunction with the right MHC haplotype, results in activation of T cells and stimulation of autoantibody production. Limitations of this GWAS included the relatively small sample size, which precluded precise localization of the risk alleles within each locus. Particularly, the origin of the signal within the MHC locus remained unclear,[8] because this region has a very complicated structure, and class I and class II response loci may each contain multiple independent haplotypes with opposing effects on risk of disease. These findings thus required follow-up in larger cohorts and validation beyond European populations.

In this issue of *JASN*, Lv and colleagues genotyped 1112 Chinese patients with MN and 1020 healthy controls for the top single-nucleotide polymorphism (SNPs) in the European GWAS (three SNPs within the *PLA2R1* locus and three SNPs within HLA genes).[9] All three SNPs within *PLA2R1* were highly associated with MN, and the strongest signal emerged from the same SNP (rs4664308) identified in the European GWAS. The HLA-DQA1 SNP (rs2187668) also showed association with MN, whereas two other HLA-located SNPs showed no such association with disease. Thus, this study robustly replicated the genetic signal demonstrated in a GWAS of European cohorts. However, in this Chinese population, the odds ratio for MN associated with homozygosity for both risk alleles was 9.9 (95% CI, 1.1 to 91.9), which is much lower than the odds ratio described for Europeans. Interestingly, the odds ratio rose to 11.1 (95% CI, 6.5 to 19.2) when looking at patients homozygous for the *PLA2R1* risk allele but either homozygous or heterozygous for the HLA-DQA1 risk allele. Similar findings have been reported in replication studies from Korea[10] and Taiwan[11]; the lower odds ratio in Asians suggests true differences in effect size between different ethnicities but may also reflect convergence to the mean. Because