has been reported in several other countries. Thus it would be interesting to see if possible contributors such as differences in major pre-ESKD comorbidities or earlier discontinuation of dialysis is more common among majority groups in other settings and might represent a universal finding, or if some of these observations are unique to America. The biologic effects of racism have been reported to be mediated through stress and the associated acute and chronic neurohormonal, physiologic, and genomic changes that affect health status. This is likely to occur in nondominant groups in other nations as well, where there is overt racism toward nondominant racial or ethnic groups.

The cause of increased rates of early discontinuation of dialysis among white relative to black patients on dialysis needs further exploration. Expectation of financial/job security and a lower standard of living than their parents, coupled with a constantly reinforced message through media of an expectation of having an even better quality of life has contributed to a sense of loss and despair for many white Americans, thought to contribute to a recent increase in premature morbidity and mortality. Such beliefs and sense of despair or loss of hope may also influence the earlier desire to discontinue dialysis reported by Agunbiade et al., in comparison with populations that have no such expectations. Indeed it has been speculated that black patients on dialysis and their families have superior coping mechanisms due to exposure to other adverse socioeconomic stressors throughout life, including dealing with inequality and discrimination. It is possible, although not yet unequivocally proven, that hardship in life allows better perception of hope in the face of difficult circumstances. To that end, black patients on dialysis and their family members may be less willing than their white peers to stop dialysis upon each hospitalization for dialysis and their family members may be less willing than their white peers to stop dialysis upon each hospitalization for dialysis and their families have superior coping mechanisms due to exposure to other adverse socioeconomic stressors throughout life, including dealing with inequality and discrimination. It is possible, although not yet unequivocally proven, that hardship in life allows better perception of hope in the face of difficult circumstances. To that end, black patients on dialysis and their family members may be less willing than their white peers to stop dialysis upon each hospitalization for dialysis and non-dialysis-related events. Also, culturally sensitive palliative care may not be consistently available to black patients on dialysis. Notwithstanding the above speculations, the issue of racial and ethnic differences in dialysis survival is rather complex and dynamic and many factors may be changing over time. However, a better understanding of these factors can lead to important insights into potential treatments that should be applicable to all groups.

DISCLOSURES

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Pilot Trials in Nephrology: Establishing a BASE for Large-Scale Randomized Trials

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Randomized controlled trials remain the only way to reliably assess moderate treatment effects because they are the study design that best safeguards against bias due to residual or unmeasured confounding. However, there have been fewer randomized trials in nephrology to guide treatment decisions than most other internal medical specialties. As a result, many commonly used treatments remain untested and the benefits and harms of these interventions remain uncertain. Increasing the quality and quantity of trials is crucial to achieving better kidney care and has been identified as a priority for the international nephrology community.

The design and conduct of kidney trials can be challenging for many reasons. Sample size and power calculations are underpinned by a number of assumptions which may not hold true despite best estimates. Because kidney failure typically develops over a long period of time, studies seeking to identify effects on this outcome require long follow-up and, until recently, there has been little consensus among investigators, funders, and regulatory agencies about other appropriate kidney function–based outcomes. Compared with the general population, medication dosing, tolerance, and adherence often differs in patients with CKD who have a high burden of illness and rate of adverse events. Recruitment for kidney trials is also often challenging due to limitations in coordinated global trial networks and infrastructure.

The net result is threefold. Firstly, most trials in kidney disease have been too small or short to detect moderate-sized treatment effects on patient-level outcomes that could be expected from any single intervention. Secondly, the outcomes which have been reported have been too varied and frequently not aligned with patient or caregiver priorities: a shortcoming which is (rightfully) being addressed by the SONG (Standardized Outcomes in Nephrology) initiative. Thirdly, many well designed trials set out with good intentions, but are unsuccessful due to unanticipated challenges in recruitment, adherence, outcome rates, or other factors.

Identifying and addressing potential scientific, operational, and implementation challenges is crucial to ensuring that a large-scale outcome trial provides a reliable answer to the question being studied. Carefully conducted and reported pilot trials are an important way to ensure such challenges and potential strategies to address them are “road tested,” which can then be adjusted before the main trial, and provide invaluable information that can be instructive for future studies.

The BASE (Bicarbonate Administration to Stabilize eGFR) pilot trial is one such example, which paves the way for a definitive large-scale outcome trial. Previous small trials have collectively suggested that bicarbonate supplementation may prevent progression of CKD, but these studies have been too small, have commonly been single center, and/or have had other limitations that mean they cannot adequately guide treatment. In this edition of JASN, Raphael et al. conducted a multicenter pilot study to assess the tolerability, safety, and pharmacodynamic profile of two doses of sodium bicarbonate over 28 weeks. The investigators randomized 194 patients with stage 3 CKD to two different dosages of bicarbonate (0.5 or 0.8 meq/kg lean body wt per day) or matching placebo and found that both bicarbonate dosages were well tolerated, with no difference in gastrointestinal symptoms or hospitalizations compared with placebo. Moreover, BP and body weight were similar at 28 weeks, with no increased use of antihypertensives or diuretics in participants treated with bicarbonate. The authors concluded that higher-dose bicarbonate might be preferred in a large outcome trial, based on similar tolerability, lower urinary ammonium excretion and higher serum bicarbonate. The BASE trial therefore provides important data to help guide dose selection in future trials of bicarbonate supplementation in CKD.

Other recent examples of valuable and informative pilot trials include BLOCADE (β-Blockers to Lower Cardiovascular Dialysis Events) and PHASE (Pilot Trial of Hemodialysis Patients undergoing Aldosterone Antagonism with Eplerenone). BLOCADE was a multicenter feasibility trial that aimed to assess the proportion of patients receiving hemodialysis who could tolerate carvedilol at a dosage of 6.25 mg twice daily during the run-in period. The trial was unable to recruit its planned sample size, suggesting that a subsequent larger outcome trial was unlikely to be feasible. The PHASE trial tested whether eplerenone was noninferior to placebo in patients receiving hemodialysis for the outcome of discontinuation due to hyperkalemia or hypotension. The trial showed no significant difference in discontinuation rates, suggesting a large outcome trial could be feasible. The results of the PHASE trial have been critical in establishing the ACHIEVE (Aldosterone Blockade for Health Improvement Evaluation in ESKD) trial, which aims to recruit approximately 2750 patients receiving dialysis to assess the effect of spironolactone on a primary outcome of cardiovascular death or hospitalization for heart failure.

Some challenges, however, cannot be anticipated. The RADAR (Reducing Residual Albuminuria in Subjects with Diabetes and Nephropathy with Atasentan) trial helped to successfully define the optimal dose of the endothelin-receptor antagonist atasentan to lower albuminuria without increasing the risk of fluid retention. The subsequent outcome trial, SONAR (Atasentan and Renal Events in Patients with Type 2 Diabetes and CKD), ultimately showed that atasentan can slow the progression of kidney disease due to type 2 diabetes, but was still challenged by lower-than-expected event rates. Although it was not possible in this case, pilot trials can also help to set realistic expectations regarding outcome parameters, as well as recruitment and retention.

As a stretch goal, it has been proposed that 30% of all patients with CKD should be enrolled in randomized controlled trials by 2030. Pilot trials are a crucial study design to help achieve this goal. It is important that the kidney community,
funding agencies, and nephrology journals prioritize such studies as valuable contributions.

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When Less Becomes More: Life and Losses without the ‘Roids’

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Despite short-term successes and a marked reduction in the overall incidence of acute rejection, long-term allograft survival after kidney transplantation has remained largely unchanged for the past three decades.1 Less than 50% of our transplant recipients have survived with a functioning graft 15 years after transplantation. The most important outcome of transplantation from the patient’s perspective is the survival

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