The idea of health-related quality of life (HRQOL) is not new. In 1946, the constitution of the World Health Organization defined health as “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity” (1). Today, the HRQOL concept addresses the effects of individual health (including the effects of both disease and its treatment) on physical, cognitive, and social functioning in day-to-day life. Patients with ESRD who are treated with dialysis experience many threats to HRQOL, both from the myriad symptoms of ESRD itself and from the physical and mental burden of dialysis treatment. For these patients, the careful assessment of HRQOL can help guide provision of medical management to optimize their health experience (2).

Although HRQOL cannot be measured directly, items that capture the patient-valued attributes that comprise HRQOL have been incorporated into reliable and valid instruments such as the generic and widely used Medical Outcomes Study questionnaires (3,4). In addition, instruments like the Kidney Disease Quality of Life (KDQOL) questionnaire (5,6), which provides generic physical component and mental component summary scores (7) as well as scores on kidney disease-specific domains, have been developed specifically for patients with kidney disease. Studies using these or similar instruments have shown that dialysis patients, compared with the general population, have poor HRQOL, particularly as measured by its physical components; in addition, lower HRQOL is associated with increased risk of mortality and hospitalizations among dialysis patients (8–10). Thus, measurement of HRQOL is an important way to assess the effectiveness of preventive and treatment strategies, such as the enhancement of hemodialysis (HD) with hemodiafiltration (HDF).

HDF combines high-flux HD with ultrafiltration of large amounts of plasma water, using convective transport to enhance removal of larger molecules. In the Convective Transport Study (CONTRAST), a randomized controlled trial (RCT) of HDF versus low-flux HD, overall there was no benefit for HDF in reducing the primary outcome of all-cause mortality (11). However, HDF did lower β2 microglobulin and phosphorus levels to a greater extent than low-flux HD in the CONTRAST study (11), and other studies have shown that HDF may reduce episodes of intradialytic hypotension (12). These benefits of HDF could potentially translate into decreased β2 microglobulin-related amyloidosis and joint pain (13), physical functioning, or other improvements in quality of life.

In this issue of CJASN, Mazaireac et al. examines the effects of HDF versus low-flux HD on the prespecified secondary outcome of HRQOL of the CONTRAST study (14). The authors measured HRQOL using the KDQOL-SF (5,6) and used a multilevel model to assess differences in changes in HRQOL domains, accounting for clustering of effects over time and within patients. Although the authors state that 93% of the KDQOL-SF surveys were filled out over time, the number of patients with known HRQOL was 681 at baseline and decreased to 512, 309, 180, 85, 40, and 14 patients in successive years, due to deaths, transplants, and relocations; however, a substantial proportion appeared to be lost to follow-up.

As has been described in previous studies, both groups at baseline had poor physical functioning (mean physical component summary score 40 ± 10 in HD patients and 39 ± 11 in HDF patients; 50 represents mean of the general population), whereas mental functioning was similar to the general population. Over a median follow-up time of 2.0 years, there were no significant differences in changes in overall HRQOL score or any particular domain between the HDF and the low-flux HD group. Both groups experienced a small decrease in the domain of patient satisfaction, although the decreases of 2.5 and 1.4 points may not be of clinical relevance, because a difference in HRQOL of ≥ 5 points has been considered by some to be clinically relevant (3). Statistically significant decreases in a variety of domains over time were observed in each group but were of even smaller effect sizes and likely of no clinical relevance. The strengths of this study include the use of a validated HRQOL instrument, repeated measurements of HRQOL over time, and the large multicenter prospective randomized design of the study. The authors point out that potential limitations may include lack of generalizability in the setting of a RCT, as well as the possibility that some individuals needed assistance filling out HRQOL forms, which could have introduced misclassification bias in the outcome measurement. However, it does not seem likely that either of these factors would differentially affect either treatment group, given the randomization, but may have biased results toward the null. There also is the possibility that losses to follow-up or transplantation may have led to selection bias, particularly because the proportion lost in the low-flux
HD arm was slightly higher than that in the HDF arm at each annual assessment.

Despite these limitations, this study is by far the largest RCT to compare the effects of HDF versus low-flux HD on HRQOL, and the authors also nicely summarize the results of previous studies (14). One single-center RCT (n=38 in the HDF group) reported better self-reported physical well-being compared with high-flux HD using a self-developed HRQOL instrument (15), whereas another single-center randomized trial (n=24 in the hemodiafiltration group) reported no difference in physical functioning using the Kidney Disease Questionnaire (16). Considering the findings of this much larger multicenter randomized trial, it seems safe to agree with the authors that HDF is unlikely to improve HRQOL in a substantive manner.

Whereas HDF does not seem to improve HRQOL, other renal replacement therapy options may have particular advantages (17) (Figure 1). A meta-analysis of observational studies comparing renal replacement therapy modalities found that patients on peritoneal dialysis (PD) had greater well-being than patients on in-center HD although differences could have also been attributable to baseline patient characteristics (17). Wu et al. rigorously examined HRQOL in incident HD and PD patients in a prospective multicenter observational study and found that after 1 year of dialysis, overall HRQOL outcomes improved for both modalities, but there were some distinct advantages for both HD (physical functioning, sleep, sexual functioning) and PD (better finances) (18). Perhaps most promising are recent studies on more frequent or nightly dialysis (19,20). One small RCT found that individuals randomized to in-center hemodialysis six times per week had improved self-reported physical health compared with those randomized to conventional in-center hemodialysis three times per week although objective measures of physical performance were no different (19). A recently published prospective cohort study showed that individuals treated with at-home short (six times per week) dialysis had a 4-point improvement in mean physical component score after 12 months (20). However, this study did not have a control arm to exclude a placebo effect, and home daily dialysis may not be acceptable or practical for some patients. Moreover, major changes in the current reimbursement structure as well as dialysis staff and resources would be needed to increase implementation of daily dialysis (21).

Beyond dialysis modalities, interventions focused on domains that are particularly poor in ESRD could be very helpful in improving HRQOL (Figure 1). Poor physical functioning is well recognized in individuals with ESRD and interventions aimed at improving mobility and strength could be beneficial in improving HRQOL (22,23). Partial correction of anemia with the use of erythropoietin-stimulating agents (ESAs) appears to improve physical functioning, vitality, and energy (24,25). Although some have argued that ESA use should be individualized as much as possible to improve patient-perceived HRQOL (26), targeting higher hemoglobin levels with ESA use has not been shown to improve HRQOL and may increase risk of stroke (27,28).

Depression exists in 20%–30% of ESRD patients, whereas sexual dysfunction exists in nearly half of ESRD patients; both are often under-recognized by providers and researchers and offer opportunities for improvement in these symptoms and consequently of HRQOL (29,30). Problems with sleep are very common in ESRD (up to 40%–80%) and range from insomnia and sleep apnea to restless leg syndrome (31,32). Indeed, poor sleep is itself a predictor of mortality and QOL (33). Significant improvements in sleep apnea have been documented with the use of nocturnal HD and cycle-assisted nocturnal PD (34,35). Preserving residual

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**Figure 1.** Possible routes of health-related quality of life (HRQOL) improvement for in-center hemodialysis patients. Alternate therapies that are associated with better HRQOL compared with in-center hemodialysis (top left) should be considered. Provider-level strategies could increase HRQOL through improved patient clinical status (top right). Interventions at the patient level (bottom) could help improve HRQOL both directly and through increased patient adherence and willingness to try alternate treatments.
kidney function has also been associated with better HRQOL (36) (Figure 1). Because most of the above findings are supported by observational data only, RCTs are urgently needed to determine if interventions in these areas can improve HRQOL.

Considering the growing number of individuals receiving home-based care for ESRD, the burden of dialysis is often shared with family and caregivers, which may lead to increased stress for everyone involved (37). Interestingly, spiritual beliefs and perception of social support networks are associated with patient-reported HRQOL (38), and dialysis patients who have the most social support were found to have greater 1-year satisfaction and HRQOL as well as fewer hospitalizations than those with poor social support (39). Interventions focused on providing resources for patients and their families including greater social support and increased self-efficacy (40) may provide another avenue for improving the HRQOL of ESRD patients (Figure 1).

In conclusion, there are several opportunities for improvement in the HRQOL of patients on dialysis, outside of dialysis prescriptions. More importantly, we must also remember that transplantation still remains the most effective form of renal replacement therapy for improving HRQOL for our patients (17), and it should be our imperative to ensure access for those eligible to undergo a kidney transplantation.

Disclosures
None.

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